Brit. J. Ophthal. (1952) **36**, 337.

COMMUNICATIONS

LAMELLAR CORNEAL GRAFTS*

CLINICAL REPORT ON 62 CASES

BY

B. W. RYCROFT AND G. J. ROMANES

From the Corneo-Plastic Unit and Eye Bank, Queen Victoria Hospital, East Grinstead, Surrey

DURING the last 100 years the pendulum of surgical fashion in keratoplasty has vacillated between partial and full thickness grafts. In the latter half of the 19th century opinion had become divided on choice of method, not as to-day because of the different applications of the two methods, but because of the relative risks which then arose mainly from infection. Between the two world wars the impetus had begun to swing towards full thickness grafts with due appreciation of the formidable risks involved, but to-day that swing now tends again towards grafts of partial thickness.

These vagaries of fashion, however, have taught modern surgeons to retain open minds, and it is now accepted that both methods have a place in the surgery of keratoplasty: for some corneal defects, such as conical cornea or descemetocoele, a full thickness graft is the method of choice, whereas for superficial corneal scars or epithelial dystrophies a graft of partial thickness is more satisfactory.

This report concerns a series of 62 cases of lamellar keratoplasty performed in sequence at East Grinstead without any attempt to select those cases likely to give better results than others. The object was to establish a technique, based on that of the Franco-Swiss School, which should be applicable to conditions in Great Britain, bearing in mind the problems of untrained personnel, immature technique, donor difficulties, and shortage of special instruments.

PERSONAL COMPARISON OF THE TWO METHODS OF KERATOPLASTY

(1) INFECTION.—Initial infection of lamellar grafts was not seen in this series. In early cases local and general penicillin was used as a routine but now only local penicillin is used in the pre-operative stage.

There were four cases of late interstitial abscess which appeared as a tiny yellow spot of infiltration in the graft bed about 4 weeks after operation. Such an abscess could hardly have been due to infection at the time of operation but aerial contamination of the graft bed is a possible cause. Tiny threads of gauze, granules of talcum powder, and globules of paraffin oil have been detected on slit-lamp examination between the graft and the

* Received for publication January 21, 1952.

bed: foreign elements which must have got there at operation. They have been seen to remain for months without causing any reaction or local infiltration. As a result of these observations great importance is attached to spray lavage of the graft and graft bed before the graft is placed in situ, and aerial contamination is prevented by cover during operation. The whole donor eye is also washed in 1 per cent. Cetavlon solution to remove the liquid paraffin after it has been taken from the container. No dry wool swabs or free gauze edges are allowed to come near the eye and each graft is also meticulously cleansed in this detergent before application. Barraquer Moner uses a small marten-hair brush which is very suitable.

To avoid contamination by talc, rubber gloves are no longer used, since although the air in the theatre is conditioned both before and during the operation, aerial suspension is always possible. Contaminants must not be confused with tiny clusters of epithelial " pearls " which are seen underneath the graft and which result from epithelial inclusion at operation. In recent cases no foreign-body contamination was noted.

In a series of penetration grafts (1933–1938 and 1946–1951) no immediate infection occurred. One patient with a penetration graft with a small anterior synechia had the misfortune to injure his grafted eye 3 years after operation with consequent infection and panophthalmitis. This case is important in emphasizing that all anterior synechiae should be removed from penetrating grafts as soon as possible after operation even though the eye is quiet. In this case the graft had been clear for 3 years.

Keratitis and iritis, except in mild form, were not encountered in this series of lamellar grafts.

(2) SCAR REPLACEMENT.—This comparison is closely related to the selection of cases. By narrow beam and wide angle slit-lamp examination with special attention to the edges of the scar, it is generally possible to estimate the depth of the corneal involvement. Retro-illumination helps to give an idea of the density, and transillumination is valuable to outline pupil shape, movements, and adhesions when a dense corneal scar is present: it has not been found to be of much value for the prediction of lens changes.

In epithelial dystrophies or scars of neurotrophic keratitis there is little difficulty in estimating the extent of the scar, but in disciform or interstitial types the problem is not easy and can often be settled only at operation. If at operation scar tissue is found to extend to Descemet's membrane a lamellar graft will not be fully effective, though it may in course of time improve residual scar tissue and corneal clarity by local tissue stimulation. There is no doubt that there is considerable evidence to support Filatov's contention that scar areas adjacent to homo-grafts do tend to clear in time, and this is a factor which can help in the ultimate prognosis of lamellar grafts.

In lamellar grafts the area of the graft can be varied up to 10 mm., but in penetration grafts 6 mm. is considered to be the optimum size because with larger grafts it is difficult to get a water-tight joint. Also, lamellar grafts

have the advantage that they can be repeated without risk and can be used to prepare the area prior to a penetration graft. Again, lamellar grafts have more scope than penetration grafts, for they may be employed not only for improvement of vision but also for the treatment of acute forms of keratitis and for reconstruction. In our experience a cosmetic tattoo of a corneal leucoma is vastly improved by the addition of a lamellar overlay graft. In this Unit a lamellar case stays in hospital about 14 days whereas a penetration case remains for one month.

(3) OPERATION RISKS.—There is no doubt that the operation of penetration keratoplasty is one of considerable difficulty requiring long practice and meticulous technique if good visual results are to be obtained. Lamellar keratoplasty is not quite so difficult in technique but requires experienced judgment.

(*a*) *Iris Inclusion.*—In a penetration graft the possibility of iris inclusion is always a hazard, and neither miosis nor mydriasis is a sure preventative. The iris may adhere to the section in small penetration grafts by the rim (pupillary anterior synechia): in larger grafts the collarette may stick to the section if miosis has been used (stroma anterior synechia), and in some cases there may be a peripheral anterior synechia to the rim of the host cornea. It is, perhaps, this complication more than any other which has forced surgeons to examine the possibilities of lamellar keratoplasty. Iris prolapse, apart from direct injury to the eye by the patient, depends on a leaking suture line, and the larger the area of the graft the more likely is this complication to arise. It is as true in penetration graft surgery as in cataract surgery that the quality of the section is of paramount importance and determines the early re-establishment of the anterior chamber: the accurate fit of the graft in a clean-cut section is the surest way to achieve an immediate seal. In the mushroom combination the central perforation should be small, and the lamellar overlay helps to seal the anterior chamber quickly. This type of graft invests penetration with a larger margin of safety and is likely to have many applications in future graft surgery.

(*b*) *Secondary Glaucoma.*—In lamellar cases this complication was not encountered where the pre-operative tension was normal, but in penetration cases there were many examples before the practice of the early removal of anterior synechiae became routine. Where there is moderate tension during a lamellar keratoplasty, puncture of the anterior chamber at the limbus or the pre-insertion of a needle will help the graft to settle into place.

(*c*) *Graft Displacement.*—Occasionally at first dressing a slight displacement of the graft was noticed, and it is thought that this was due to the overlay stitches being tied too tightly: this is of no great consequence, however, as the tiny gutter epithelializes with no ill-effects.

In three cases total displacement occurred, but again in lamellar keratoplasty this is not a catastrophe. One case occurred in a cosmetic tattoo, possibly because the graft did not " take " on the tattooed graft bed; another occurred through direct injury by a young patient rubbing his eye underneath the bandage, and the third as a result of diminished fibroplasia when full systemic cortisone therapy was

being used in an early trial. The graft was entirely free and no sign of reaction was present.

In cases of total displacement, a replacement can immediately be done if a donor is available, or else epithelialization can be allowed to occur with a view to another formal keratoplasty later.

In a penetration graft, on the other hand, displacement is a major tragedy which may lead to lens loss or secondary glaucoma. In an early series two grafts were displaced: one was the result of severe post-operative vomiting where general anaesthesia had had to be used, and the other was due to straining in acute retention of urine. Primary direct sutures were not then in vogue, but were used to repair the grafts in these two cases; both grafts healed well but remained opaque.

(4) GRAFT OPACIFICATION.—Three types of opacification have been recognized as common to both methods of keratoplasty:

Early opacification from reaction oedema in the immediate post-operative period usually clears by the second week: it appears to spread from the edge of the graft to the centre and clears in a similar fashion. It is not associated with much vascularity and the eye is quiet.

More serious is the opacification which never really clears and in which the vascularity steadily increases after the first week. This is the type of vascularity which shows excellent control with intensive local cortisone; the graft then clears in most cases but occasionally the vascularity increases and much fibrosis occurs. It is thought that allergy is responsible for this small group which does not respond to treatment.

Thirdly, there is graft malady, which is a constant menace up to 3 months after operation: the malady will come on about 3 or 4 weeks after operation in a graft which has appeared to be successful and clear. It is characterized by rapid massive vascularity which itself is largely the cause of opacification.

One is forced to the conclusion that in many of these cases an antigen immunity reaction must be a causal factor. In this connection the work of Klima (1949a) merits further attention. Using rabbits and corneal extracts, he showed that in one group (when corneal extracts were injected into the other cornea of the same rabbit) no reaction was produced, indicating that tissue damage itself was not the cause of the reaction. In the second group (where other rabbits were injected with corneal extracts) eighteen cases out of 45 showed vascular reaction. Klima claims that these results show immuno-biological differences between host and donor and that it is pure chance whether this relationship is encountered or not.

Since this uncertainty exists, it is considered wise to treat all corneal graft cases with post-operative antihistamine therapy: cortisone has lately been used as routine local application after the first week in an attempt to block this reaction. The other treatment of neo-corneal vascularization includes shock therapy with T.A.B. injections, which probably depends for its advantageous results on the stress release of ACTH and retrobulbar alcohol-xylocaine injections which abolish axon reflexes and help to quieten the eye.

Pre- and post-operative *x*-radiation has not been decisive because it has been found difficult to form any conclusions in the absence of accurate control.

Much work remains to be done in the investigation of the allergy factor: it may be dependent on the age of the graft or on tissue sensitivity, and there may be some parallel relationship with the survival of homo skin grafts or with lens protein reactions.

TECHNIQUE

In lamellar keratoplasty the technique of Paufique and his colleagues has been followed and it is unnecessary to describe it here in detail as it is so well known. Occasionally this technique has been modified at East Grinstead owing to the difficulty of obtaining special instruments or on account of personal taste.

Preliminary Preparation Anaesthesia.—For many years preliminary sedation by luminal (gr. 3 in adult cases one hour before operation) combined with the use of ear packs to shut out ward noises has been satisfactory. All conjunctival irrigations and preliminary cocaine instillations are completed before transport to the theatre so that disturbance is reduced to the minimum and the patient arrives in a calm and tranquil state.

Penicillin drops are used for 3 days before operation: a sticky over-night pad is an absolute indication for the postponement of the operation and more attention is paid to this feature than to the results of a conjunctival culture. In the theatre quietness is the rule and becomes absolute after the patient has been rehearsed in eye movements and given final instructions. As stated before gloves are not used, but the hands are washed and finished with 1 per cent. Cetavlon solution and dried off in spirit.

Anaesthesia is commenced one hour before operation and is by local 4 per cent. cocaine with adrenaline drops. Retrobulbar injections are not now used in lamellar cases as it is felt that a softened globe has occasionally hindered an accurate trephine section. A dilated pupil is preferred in case a mushroom graft may have to be carried out. In view of the tendency of the pupil to dilate under cocaine-adrenaline anaesthesia it is felt that dilatation and the risk of lens damage is preferable to miosis and the occurrence of an anterior synechia in the event of adventitious penetration. Facial akinesia by the O'Brien method and superior rectus infiltration with a retraction suture are routine. Lid retraction is by sutures, Desmarres' retractors, or Barraquer's speculum. The work of Barraquer Moner in the use of curare to avoid facial block and retrobulbar injection is of great interest and this method is now under trial.

Preparation of Graft Bed.—After trial of many needles, the 5-7 mm. Barraquer corneal needle (Grieshaber) is now exclusively used. This needle is so sharp that fixation of the globe is generally unnecessary and only light counter pressure is required. All points and cutting edges of instruments have been previously examined on the slit lamp before operation, as advised by Arruga, and this procedure has certainly prevented trouble.

Since our practice is now to use large lamellar grafts, fixation is by overlay retention sutures at the limbus or by direct sutures: it appears to be of little consequence whether the suture is atraumatic or not. For overlay stitches two contra-lateral insertions are made and the spread of the suture is adjusted by the travel of the needle in corneal tissue; four insertions per suture are no longer made. The pupil centre is marked with a pen dipped in Bonney's blue and the extent of the scar is measured with calipers. A suitable size of Franceschetti trephine is selected, and with increasing experience larger sizes (8-10 mm.) are now being used. The depth is set according to the lesion, *i.e.*, shallow for epithelial dystrophy and deep for a burns scar; fixation of the globe is by Von Mandach or Barraquer forceps. It is most important to inspect the relationship of the cutting edge of the trephine to the edge of the piston. It has been noted occasionally that after a trephine has been resharpened these two edges were not parallel, and as a result there

is a likelihood of unequal depth penetration. Just as in cataract surgery, where the initial section is of such importance, so here great care must be taken to centre the trephine exactly.

The next important step in the excision of the corneal disk is to start the section at the pre-determined level so as to keep to the same plane across the base of the graft bed. A miniature Desmarres' blade without corners and set at an angle to the shaft has been designed for this purpose (Fig. 1). Once the plane of separation has been determined, the disk should be separated by smooth strokes rather than by small irregular cuts. The new pyriform knife of Barraquer Moner helps this manoeuvre considerably. As the disk is split it is lifted with a pair of fine-tooth forceps (Jayle, Castroviejo, or Sobhy Pasha pattern), but it must not be stretched or there is a risk of tenting Descemet's membrane and opening the anterior chamber adventitiously. The disk should be removed in one piece of even thickness, but when the scar is soft and friable this is not always possible.

Attention is next given to the graft bed, which is accordingly cleared to an even

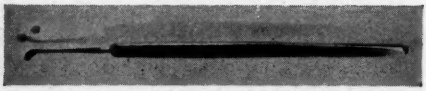


FIG. 1.—Modified Desmarres' knife.

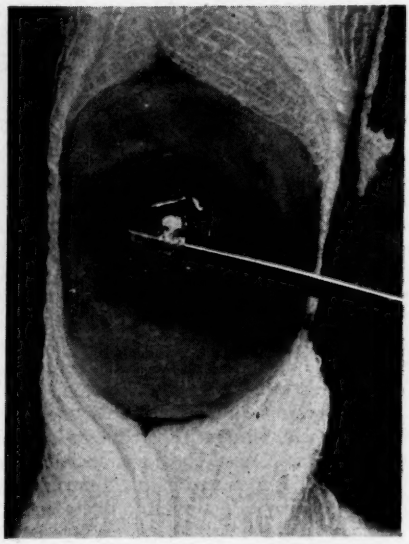


FIG. 2.—Residual scar is seen in the base of the graft bed. A narrow Graefe knife is passed through the scar and cuts out so as to make a free edge which can be gripped by forceps without risk of penetrating the anterior chamber.

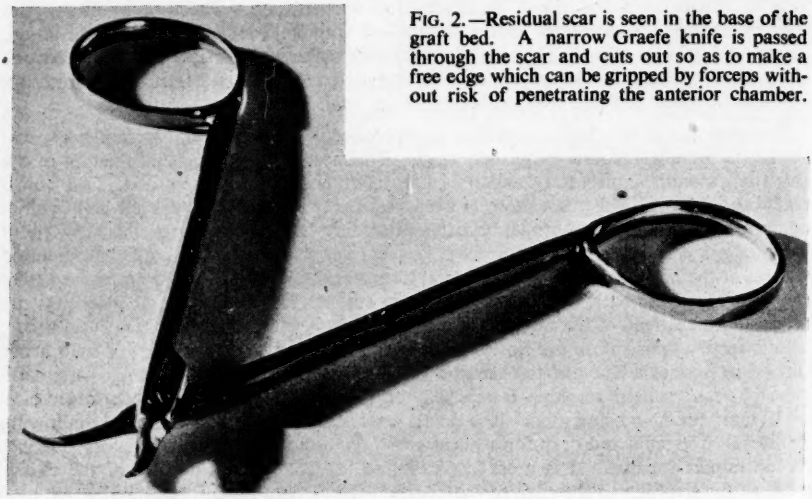


FIG. 3*a*.—Graft scissors are curved on the flat with a serrated edge along one blade (Down Bros.)

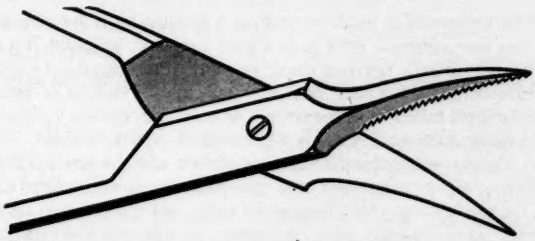


FIG. 3*b*.—Diagram (by courtesy of Mr. Robin Dale, F.R.C.S.) showing serrations pointing towards the hinge, which are difficult to demonstrate in a photograph.

depth at the edges: haemostasis with heated probe must be complete. Professor Offret demonstrated a useful method of removing remaining fine bands of scar tissue from the graft bed which could not be picked up with forceps. A 1.5-mm. Graefe knife is slid under the band, which is excised and so given a free edge which can be picked up with forceps (Fig. 2). To trim the edges of the bed or of the graft, special scissors have been designed in which one edge is serrated towards the hinge: this prevents elastic corneal tissue from slipping away from the bite, a nuisance which occurs especially in penetrating grafts (Figs 3*a* and 3*b*) When the preparation of the graft bed is complete the lids are pulled together and the graft is prepared.

Graft Preparation.—After many trials a graft is used of diameter 0.1 mm. less than the bed. A Gillette blade 'A' (Fig. 4) is used to obtain small grafts, and a Desmarres' knife enables larger grafts to be prepared. By regulating the pressure of the excised globe with the holding fingers the graft can be smoothly sawn off. It is important that the

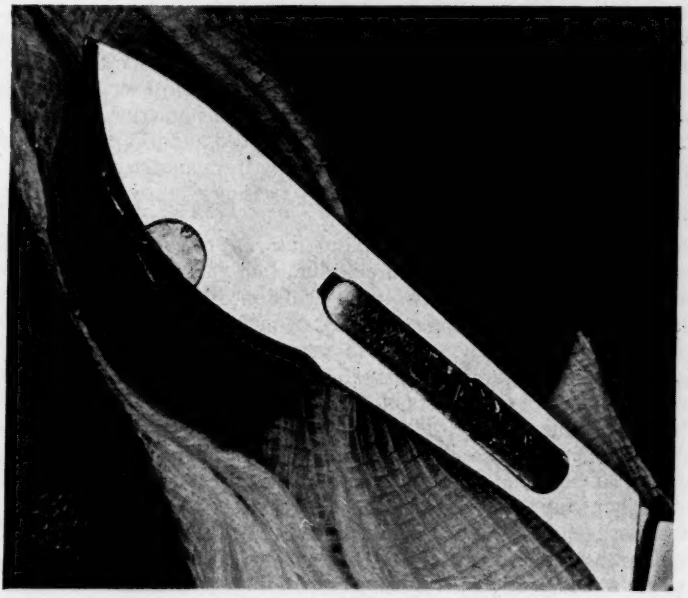


FIG. 4.—Excision of 6-mm. lamellar graft by large Gillette Blade A.

graft should not be immersed in fluid for long, as a swollen graft leads to an innacurate fit. After the graft has been sprayed with 1 per cent. Cetavlon solution it is placed between layers of moist gauze where it remains damp but not waterlogged. Grafts from different levels of the donor cornea have been used with success. The loss of epithelium is of no consequence, and a graft taken from the stroma of the donor cornea without any membrane (sandwich graft) takes quite well in normal position or upside down.

The graft bed is also well sprayed to remove debris and the graft is placed in position by firm moulding; air is expressed and the contour is the guide to a satisfactory placement. If the graft is too thick it must be split, and if Descemet's membrane bulges too sharply the anterior chamber must be tapped, though this has rarely been necessary. The surgeon waits and satisfies himself that the graft is adherent and in the proper position before the egg membrane is applied. The overlay stitches are carefully tied so as not to disturb either membrane or graft. No atropine or eserine is used in uncomplicated cases.

In this Unit graft cases remain undisturbed for a week, as it is felt that early dressing may irritate the eye and either aggravate initial vascularity or delay epithelialization. French colleagues, on the other hand, successfully dress their cases on the 3rd or 4th day. At the end of a week double pads and stitches are removed: a single pad is retained for a few days until 2 clear days have elapsed without fluorescein stain. Anti-histamine therapy (Thephorin (Roche)) is given for 14 days in an endeavour to control the antigen reaction of host-donor corneal tissues. Massive doses (5 g.) of vitamin C are also given following the advice of American authors; where there is undue abdominal discomfort vitamin C is given by injection. Cortisone drops are begun, if healing is satisfactory, on the 8th day. Lamellar grafts are discharged from hospital at the end of 14 days but such grafts are not considered safe until one month after operation has elapsed. Occasionally in the 2nd or 3rd week a small erosion of epithelium occurred, but this healed quickly when the eye was covered for 48 hours.

Complications

(*a*) *During Operation.*—It cannot be too strongly emphasized that a careful slit-lamp examination of graft instruments before beginning the operation will go far in preventing difficulties during the operation. The most serious complication in lamellar keratoplasty is the accidental opening of the anterior chamber. If the penetration is early in the preparation of the graft bed and if it is on the periphery it may be possible to remove the disk by starting from another direction. If it is late, a mushroom graft may be performed by excising a central 4-mm. area of the graft bed. In other instances, however, it is wise to abandon the operation and to replace the corneal disk, fixing it in position by one or two intra-corneal sutures. Five examples of this procedure are included in the present series: one was completed as a lamellar graft, two were abandoned to have the operation at a later date, and the other two were converted to mushroom grafts, of which one gave an excellent visual result (6/9). When penetration has occurred atropine and mydricaine are always used. It is probable that a soft globe has misled the surgeon as to depth in some of these cases of adventitious penetration, but in mustard gas keratitis or pemphigus this is always to be expected owing to the uneven, deep crater-like deficiencies present in the corneal scars in these diseases. The conversion of a lamellar graft to a full penetration graft has not been practised in our series, mainly owing to shortage of donor material.

Haemorrhage in the graft bed should always be controlled by gentle heat cautery. It should not be a marked feature of an optical graft but it may be troublesome in cases where a therapeutic graft is being employed.

It has been found useful to surround grafts with a second larger trephine cut:

this not only checks haemorrhage but may delay vascularization. It is well known that a superficial trephine cut alone will often improve the clarity of a corneal scar, and may give the appearance of a good graft where in fact no graft has been performed.

When a band of scar tissue remains on Descemet's membrane, it is a great temptation to try to remove it. If there is a risk of penetration in a satisfactory graft bed, it has been our practice to resist this temptation, for it is surprising how wide is the variation between the improvement of vision and the presence of deep corneal scar fibrils. Sometimes a graft bed may appear to be semi-opaque by reflected light but when a drop of saline is placed on it and refraction improved the anterior chamber details may be clearly seen, indicating the likely improvement of vision in the future. It is this point of technique which requires great experience of judgment.

(*b*) *After Operation.*—Dislocation of the graft occurred in three cases in this series: all three epithelialized with satisfactory results. Early infection was not seen in any case, but in four there was the late occurrence of a solitary interstitial abscess which occurred from 4 to 6 weeks after operation. The reaction around the abscess slowly subsided but a tiny deep circular scar remained.

Vascularization remains a serious feature with lamellar grafts. Immediate vascularization up to 10 days usually settles, but when it occurs in the 2nd or 3rd week and increases in intensity it is a major problem. This delayed vascularization is of allergic origin and may correspond to the oedema when homo-plastic skin grafts are thrown off: furthermore, repeated grafts from other donors do not necessarily evoke the same reaction as the initial graft. Late vascularity of this type has been noticed in seven out of forty optical grafts in this series, and in five of the seven cases the clarity of the graft was markedly impaired.

Effect of Cortisone

There is no doubt whatever that local cortisone drops applied every hour from the 8th day have a profound beneficial effect on neo-corneal vascularity at this stage. Possibly this is to be explained by the endothelial proliferation inhibition exerted by cortisone (Ashton and Cook, 1951). In late vascularization, when vessel trunks have been established with fibrosis, cortisone has less effect. When local cortisone is used in the initial stages after keratoplasty, a careful watch should be kept on the healing edges of the graft as deepening of the gutter has been noted. The aetiology of delayed vascularity in lamellar cases is quite different from that in penetration grafts which is usually caused by adhesion of the iris to the graft.

Late observation of lamellar grafts indicates that, once a clear graft has settled and has become established in a white eye, visual improvement can be expected to continue for many months. Where late keratitis has occurred some months after successful keratoplasty, cortisone has been found to be most useful, and threatened opacification of the graft has been averted, the immediate subsidence of vascularity and the disappearance of corneal oedema being quite remarkable.

Clinical Analysis

The diseases treated, the number of patients, and the types of graft performed are tabulated below. Altogether 62 grafting operations were performed on 52 patients suffering from 14 different pathological conditions.

	Diseases	Patients	Grafts
1.	Pemphigus of conjunctiva and cornea	3	4
2.	Burns (*a*) Chemical	7	8
	Burns (*b*) Thermal	3	3
	Burns (*c*) Gas	1	1
3.	Recurrent pterygium	1	2
4.	Epithelial dystrophy of cornea	2	2
5.	Band-shaped keratopathy	5	5
6.	Acne rosacea keratitis	8	10
7.	Disciform keratitis	1	1
8.	Neurotrophic keratitis	1	3
9.	Superficial punctate keratitis	—	—
10.	Lipoidosis of cornea	4	7
11.	Interstitial keratitis	3	2
12.	Healed ulcers	8	9
13.	Leucoma adherens	3	3
14.	Active corneal ulcers	2	2
	Total	52	62

Analysis of Results

The results obtained with the four different classes of graft may be tabulated as follows :

Type of Graft	No.	Improved	No Change	Worse	Not Assessed
(1) Optical	41	24	11	4	2
(2) Therapeutic	9	6	3	—	—
(3) Cosmetic	7	7	—	—	—
(4) Preparation	5	4	1	—	—
Total ...	62	41	15	4	2

(1) Optical Grafts

Forty-one cases. The results of the optical grafts are classified according to visual improvement after operation by means of a fractional basis of percentage. Thus improvement of vision from perception of light to 6/5 represents 100 per cent., and each of the ten visual steps in between is equal to 10 per cent.; for example, 6/60 to 6/24 represents two steps and is assessed as 20 per cent. improvement no

matter where this occurs in the visual acuity scale. On this basis the 24 cases in which vision was improved by lamellar keratoplasty may be analysed thus:

Stages of Improvement	Degree of Improvement (per cent.)	No. of Cases
Perception of light to hand movements	10	7
Hand movements to counting fingers...	20	5
Counting fingers to 6/60	30	2
6/60 to 6/36	40	4
6/36 to 6/24	50	5
6/24 to 6/18	60	—
6/18 to 6/12	70	1
6/12 to 6/9	80	—
6/9 to 6/6	90	—
6/6 to 6/5	100	—

In this series of lamellar optical grafts the longest period of donor graft preservation was 21 days in a case where vision was improved from hand movements to 6/36. No direct relationship in the post-operative reaction of the graft to the length of the period of preservation was established. The best visual result was obtained in a case of acne keratitis where vision was improved from perception of light to 6/9.

Failure of Optical Grafts.—It is generally the case that a clear lamellar graft in a white eye 6 weeks after operation will continue to improve as the months go on. Late trouble is not common but it is also quite certain that the condition of the host cornea outside a successful graft will also improve by a steady clarification of adjacent scar tissue. In this series, which it must be emphasized was consecutive and not chosen for the best prognosis, the failures were due to:

(*a*) Unsuitable type of case for lamellar keratoplasty. If the scar tissue extends to Descemet's membrane a full thickness graft is the method of choice.

(*b*) Influence of the original corneal disease. Pemphigus has given consistently bad results through late vascularization and xerosis of the graft, and this also applies to penetration grafts. On the other hand, band-shaped keratopathy gives excellent results after lamellar keratoplasty.

Mustard gas cases vary, but on the whole, in our hands, the results have not so far been good.

(*c*) Unpredictable tissue allergy. This accounts for a proportion of bad results by causing severe vascularization and consequent dense opacification. It is unpredictable but may possibly be prevented or minimized by the use of cortisone, which is said to block the antigen reaction of tissues with prevention of fibrosis. Control experiments with cross skin and corneal grafts are in progress.

(*d*) Technique in early cases must always play a part. Lamellar keratoplasty demands considerable skill in manoeuvre, and in judgment of the correct plane for separation of the scar. The pre-operative slit-lamp scrutiny of cutting edges and points is absolutely imperative.

(*e*) Infection did not influence the results to any great extent.

The detailed results in the four cases which were classed as failures are tabulated below:

Case No.	Stage of Deterioration	Degree of Deterioration (per cent.)	Reason
1	6/60 to counting fingers	10	Recurrence of acne keratitis in graft. Subsequently treated by full thickness graft with vision 6/36.
2	6/18 to 6/36	20	Poor selection
3	Counting fingers to hand movements	10	Second lamellar graft in same patient as Case 1
4	6/36 to counting fingers	20	Recurrence of acne keratitis in graft

(2) THERAPEUTIC GRAFTS

Nine cases were operated. The diseases in question are tabulated below:

Disease	No. of Cases	No. of Grafts
Recurrent pterygium	1	2
Neurotrophic keratitis	1	3
Active acne keratitis	3	3
Acute epithelial dystrophy...	2	2
Active corneal ulcer	2	2

There is an expanding field for the use of therapeutic grafts in active corneal disease. They have been found valuable for shortening the hospitalization period of chronic corneal ulceration and for the avoidance of median tarsorrhaphy in indolent infections. Moreover, second-class donor material can successfully be used for therapeutic grafts. The principle is the same as that employed when indolent leg ulcers are covered by cross-leg skin flaps.

(3) COSMETIC GRAFTS

When there is a leucoma adherens in a blind eye in a young person a tattoo operation to disguise the white staring appearance is well justified. Normal practice has been used to use the platinum black method and to cover the tattooed cornea with a lamellar graft of equal size. Post-operative discomfort is reduced and the area heals quickly, giving a natural appearance. Whether this combination is more permanent will be decided by future observations.

(4) PREPARATION GRAFTS

There were five cases of this type and five grafts were done.

When the host cornea is widely and densely thickened, as in severe burns, most grafts take successfully, but speedily become opaque since it is difficult to position them so that they adjoin on normal corneal tissue. In such cases the cornea is previously prepared for a penetration graft by one or more lamellar grafts: a more accurate fit and a better site for the penetration graft are thus obtained. A preparation graft can also be employed where there is excessive vascularity of the host cornea. In one case where this was done the vascularity subsided and did not invade the graft: the graft which remained clear thus acted simultaneously as

a preparation, therapeutic, and optical remedy, and vision was improved from hand movements to 6/18 (Mrs. L.).

The Donor Problem

The increasing scope of keratoplasty demands that an adequate and regular donor supply of good material should be widely available.

As in many other countries, the donor supply is becoming a problem of increasing and urgent gravity in Great Britain.

Two solutions to this problem come to mind. As a temporary relief all present available donor supplies should be referred to hospitals which have experienced surgeons and the necessary equipment for graft surgery. All eyes which have to be excised for choroidal sarcoma, absolute glaucoma, injury, or in the course of orbital surgery represent a valuable source of donor material which should not be wasted. Such eyes should be placed in liquid paraffin immediately after excision and preserved at 4° C. in the hospital refrigerator before despatch. At East Grinstead such a scheme has worked well for over 2 years with the helpful co-operation of ophthalmic surgeons in the south of England. The Eye Bank has thus received a steady, though inadequate, supply, which has provided many successful grafts. From eyes preserved in this fashion clear optical lamellar grafts have been obtained 21 days after excision, and therapeutic grafts have been used from eyes excised 24 days previously. The permanent solution is to modify legislation by the force of educated public opinion so as to provide British surgeons with the same facilities as are enjoyed by their French colleagues who, thanks to the enlightened Decree No. 472, 057, of 1947, are able to tap a large reservoir of healthy cadaver material.

It is generally agreed that healthy eyes obtained from elderly people who have died a natural death represent the best source of donor material for optical grafts and that this source is better than the pathological material which British surgeons have to use at present.

In British law the body has no property, and, therefore, strictly speaking a person cannot bequeath his or her eyes. He can express during his life a desire to do so, but the implementation of this desire depends on the approval of the nearest relative or executor who can supersede the wish of the deceased if he objects to removal of the eyes.

Cadaver eyes should be removed within 2 hours of death, and it will, therefore, be appreciated that *post-mortem* permission generally arrives too late, and that, even then, removal of the eyes is illegal. Experience has shown that the nearest relatives are most co-operative when eyes have been bequeathed, but it is distasteful for surgeons to press for speedy excision in the presence of recent bereavement. It is good that the legal aspect of donor material has now received the serious attention of Parliament.

The important interval of time in cadaver grafts is that between death and excision: the length of the period of preservation is less important.

The Eye Bank at East Grinstead, which is generally overdrawn, receives eyes in special containers (Fig. 5). The eye is totally immersed in liquid

paraffin in a wide-mouthed glass bottle which is fixed in a copper watertight chamber and surrounded by ice. On arrival at the Bank the eye is registered and placed in a refrigerator at +4° C.: along with the eyes is also preserved skin for use in socket surgery and cartilage for contour restoration. For short period preservation saline vapour has been used, but liquid paraffin is better for transport on account of the inertia of the oil which protects the eye.

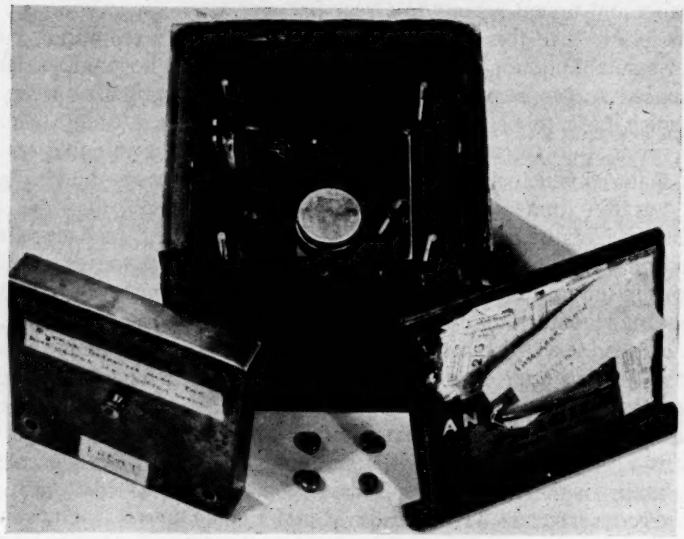


FIG. 5.—East Grinstead container for transport of donor eyes.

USE OF CORTISONE

For the past 6 months cortisone has been under trial in various ways, and thirty graft cases have been treated. It was expected to block the antigen reaction of the donor cornea, to diminish opacification of the graft, and to influence the growth of endothelium of new blood vessels. In two early cases intensive parenteral and local cortisone therapy was employed immediately after operation, but the alarming result of grafts which did not adhere was noted, and parenteral cortisone injections were, therefore, stopped.

When used, however, as local drops by hourly instillations there were two constant effects. The grafted eyes were free from discomfort, and the difference was always noticed by those patients who had had grafts with and without cortisone in the post-operation period. Furthermore, the reactionary neo-vascularization which is a feature one week after operation was constantly reduced, and it is possible that more serious vascularization was prevented.

Cortisone did not seem to affect late corneal vascularity where vessel trunks were seen and considerable fibrosis of the graft had been established, nor did the aetiology of the initial disease make any difference.

Cortisone drops are now begun on the 8th day after operation when the

stitches have been removed, and they are continued hourly for at least a week. In two cases it was thought that the graft line deepened to a gutter after local cortisone and this was taken as an indication that epithelialization was being delayed. The appearance disappeared when cortisone was stopped. There did not appear to be any special advantage of the subconjunctival route of administration over instillations.

SUMMARY

(1) Lamellar keratoplasty has many advantages of safety over penetration keratoplasty, but 30–40 per cent. of cases where defective vision is due to a corneal lesion require the latter procedure or a combination of both.

(2) In this series of sixty lamellar cases, 41 were optical grafts and vision was improved in 24 cases. The best results were those which improved from perception of light to 6/9; no change was seen in eleven; there was deterioration in four, and the change was not assessed in two. No eyes were lost and in some of the cases which were not improved a further graft, either of lamellar or penetration type, will improve vision. Contact lenses have not been used for permanent improvement of vision.

The scope for therapeutic grafts extends rapidly. The use of cosmetic grafts is under observation.

(3) A major problem which remains to be solved is that of tissue allergy. In this series ten cases showed severe vascularity which could be ascribed to antigen reaction between donor graft and host cornea.

(4) The factors which influence success in lamellar keratoplasty are the correct selection of cases suitable for this method, perfect instruments, mature technique, and adequate after-care, together with the use of first-class donor material. Late vascularization and opacification of the graft due to allergy are at present unpredictable.

(5) Cortisone instillations relieve early corneal neo-vascularization and discomfort. They may prevent more serious late vascularization.

(6) In Great Britain legislation should be amended to provide adequate donor material if the wide benefits of keratoplasty are to be fully utilized.

Any surgeon who practices lamellar keratoplasty to-day is deeply in the debt of Professor Louis Paufique and his colleagues: our share of this debt is great and in addition we wish to acknowledge with gratitude the personal help we have received from Professor Paufique, René Hugonnier, and Jacques Rougier, both at Lyons and at this Unit.

The interest and encouragement of Sir Archibald McIndoe and our colleagues at East Grinstead have been a great help, and without the skill of our nursing staff it would not have been possible to carry out this work. We are also grateful to those ophthalmic surgeons who have contributed donor material and to Doctor Allott and the authorities of the South-East Metropolitan Regional Hospital Board for making available to us supplies of cortisone. Our thanks are also due to Mr. Gordon Clemetson for his expert photography.

BIBLIOGRAPHY

ASHTON, N., and COOK, C. (1951). *British Journal of Ophthalmology*, **35**, 708.
KLIMA, M. (1949a). *Sborn. lék.*, **51**, 1.
——— (1949b). *Čsl. Ofthal.*, **5**, 37.

Brit. J. Ophthal. (1952) 36, 352.

POLYMYXIN E*

PENETRATION INTO THE EYE AND THERAPEUTIC VALUE IN EXPERIMENTAL INFECTION DUE TO *PS. PYOCYANEA*

BY

D. AINSLIE AND CHARLES SMITH

From the Departments of Clinical Research and Pathology, Institute of Ophthalmology, London

THE polymyxins are a group of five closely allied antibiotics extracted from the *Bacillus polymyxa*. *In vitro* and in the field of general medicine they have been found bactericidal to nearly all Gram-negative bacilli, and the good results obtained in combating *Ps. pyocyanea* infection of burns by the local application of polymyxin (Jackson and others, 1951) suggested the possibility of using them locally in eye diseases.

Early experiences with polymyxins A and D, and later with polymyxin C, showed that they caused damage to the renal convoluted tubules (Stansly and others, 1947; Brownlee and Bushby, 1948) and consequently they were not widely used clinically. Polymyxin B (Brownlee and others, 1949) was found to be almost free from nephrotoxic effect, but it gave rise to neurotoxic signs such as ataxia, and also led to severe irritative reactions at the site of injection.

The most recent preparation, polymyxin E, has a toxicity similar to that of polymyxin B, but does not cause irritation at the site of injection. It therefore seemed probable that polymyxin E would be suitable for sub-conjunctival injection. The general level of antibiotic in the body after this method of administration would be small and thus unlikely to lead to any neurotoxic reaction.

Eye infections with Gram-negative bacilli are not common but may be of the greatest severity. Treatment in the past has been unsatisfactory but recently good results have been reported with streptomycin therapy (Bignell, 1951; Sorsby and others, 1952). Bignell collected ten cases infected with *Ps. pyocyanea* during 1950. In his case notes he emphasizes the severity and rapid spread of the infection; he considers that pyocyanea ulcers can be recognized clinically, showing first as a dead white area in the cornea with central superficial necrosis, and later assuming the form of a white ring with a semitransparent centre. If untreated the whole cornea rapidly becomes disorganized. Sorsby also emphasizes the characteristic clinical appearance of corneal ulceration due to Gram-negative bacilli.

PROPERTIES OF POLYMYXIN

Polymyxin E is prepared as a white crystalline powder which is highly soluble in water. 1,000,000 units dissolve readily in 1 ml. Its molecular weight is in the

* Received for publication February 4, 1952.

neighbourhood of 1,000, which is about three times the size of the penicillin molecule. It is not readily soluble in lipoids and the ether-water partition ratio is low.

It has been shown by Langham (1951) that water-soluble substances with a low ether-water partition ratio appear to enter the intra-ocular fluid through the intercellular spaces of the blood-aqueous barrier, while the lipoid-soluble substances themselves pass *via* the cells. Substances with large molecules cannot pass through the inter-cellular spaces and will not therefore cross the blood-aqueous barrier unless they are lipoid-soluble.

Polymyxin E is thus unsuitable for systemic administration in intra-ocular infection, but fortunately its extreme solubility in water renders it highly suitable for subconjunctival injection, and, as will be seen, direct penetration of the coats of the eye, when given by this method, is very satisfactory. The aqueous solution, even in concentrations of 1,000,000 units per ml., causes little irritation when given subconjunctivally, though it is best to add a local anaesthetic to the solvent. Mydricaine is suitable and has the added advantage of containing adrenaline. Subconjunctival scarring as a result of the injections is minimal.

Effects of Polymyxin Injected Subconjunctivally

A single dose of 500,000 units of polymyxin (0.5 ml. of solution) was injected subconjunctivally in two rabbits. The subconjunctival bleb remained for 3 days but disappeared leaving no trace. Slight corneal oedema developed in both instances but this resolved entirely.

Two further rabbits were injected with 200,000 units (0.2 ml. of solution). The smaller subconjunctival blebs resolved in about 48 hours. The corneae remained bright throughout.

Five rabbits were given a more prolonged course, 330,000 units (0.33 ml. of solution) on 4 successive days, followed by 200,000 units on 2 subsequent days. Large subconjunctival blebs arose but settled down in from 4 to 6 days after cessation of treatment and left no trace. In one rabbit a faint corneal haze developed on the 3rd day but this had cleared entirely 2 days after the cessation of treatment. In another rabbit a small band-shaped opacity developed in the interpalpebral area. The conjunctival blebs in this case were considerably larger than in the others and the opacity appeared to be due to exposure. Had it been possible to pad the eye this would probably have been prevented. As the conjunctival oedema settled the opacity lessened, but a permanent nebula resulted. In the three remaining cases the corneae remained bright throughout.

Penetration of Polymyxin into the Eye following Subconjunctival Injection

Assay.—The assay of polymyxin in ocular fluids is difficult owing to the small volumes of these fluids which are available. Since an anterior chamber puncture will not yield more than 0.25 ml., it is impossible to use the normal serial dilution methods (Brownlee and Bushby, 1948) using 1-ml. volumes.

Our first assays were made by adding 0.1 ml. aqueous fluid to a filter paper disk and placing this on a plate seeded with the test organism. By this technique small amounts of polymyxin were detected in samples aspirated from 45 minutes to 2 hours after a subconjunctival injection of 500,000 units

of polymyxin. No polymyxin was detected before 45 minutes or after 24 hours had elapsed since the subconjunctival injection. Unfortunately the rings of inhibition of growth were small and could not be compared accurately with rings produced by standard amounts of polymyxin.

To obtain more accurate assays it was decided to use a capillary tube micro method. The technique was that described by Fleming and Smith (1947) for the assay of penicillin, except that the medium used was 1 per cent. glucose digest broth at *p*H 7.8 and the test organism was a *B. coli* strain S.1. The disadvantages of this technique have been pointed out by May and others (1947). To minimize errors the method was rigidly standardized and with each batch of fluids assayed a control assay of 100 units of polymyxin was included.

TECHNIQUE.—1 ml. of the phenol red-glucose broth medium was inoculated with *B. coli* S1 and incubated overnight. The next morning 5 cmm. of this culture were added to each ml. of medium to be used in the test. Tests were set up using 25 cmm. volumes for the serial dilutions, and it was noted that the aqueous always imparted a slightly more alkaline *p*H to the first tube of each series. Capillaries were filled, sealed at both ends, and incubated horizontally for 18 hours. In every case eight two-fold dilutions were set up.

Readings were made on the following scale:

Negative	... ...	No colour change
±	... ...	Incomplete change of colour.
+	... ...	Complete change of colour but no gas formation.
++	... ...	Complete change of colour with gas formation.

Five corneae were assayed. These were prepared as follows:

A disk of cornea was removed by means of a cork borer from an eye which had been frozen immediately after its enucleation. The disk was weighed and then ground up in saline, 0.1 ml. of buffered saline (*p*H 6.8) per mg. of moist weight.

Vitreous fluid was obtained by dividing the frozen eye immediately behind the lens; the vitreous could then be picked out as a solid mass and thawed for use in the assay.

It was found that, with strict adherence to technique, assays of standard solutions of polymyxin gave identical readings.

RESULTS

(*a*) *Aqueous.*—Twenty-five aqueous fluids were assayed, all being removed between 1 and 3 hours after subconjunctival injection of 250,000 units of polymyxin E in aqueous solution. The whole operation was performed under nembutal anaesthesia. Of the twenty-five fluids, nine showed polymyxin contents of 200 units per ml. or greater, ten from 50 to 100 units per ml., and five from 10 to 50 units per ml. No relationship between time of removal and concentration was noted in specimens aspirated between 1 and 3 hours after giving polymyxin.

(*b*) *Vitreous.*—Six vitreous fluids were assayed 3 hours after subconjunctival injection. They had a similar range to that of the aqueous fluids, the actual levels being 200 units per ml. in two cases, 50 to 100 units in three cases, and 20 units in the remaining case.

(*c*) *Cornea.*—Five corneal extracts were assayed 3 hours after subconjunctival injection. They showed a somewhat higher concentration, and, with more prolonged extraction, this might have been still greater. Concentrations were 2,000 units per g. or more in two cases, 100 to 200 units in a further two cases, and 100 units in the remaining case.

Treatment of Experimental Corneal Infection

It was decided to assess the value of polymyxin in pyocyaneus corneal infections produced experimentally since the cornea is the area most commonly found to be infected by this organism in ophthalmic practice.

Inoculum.—The organism used to produce the eye lesions was a stock laboratory strain No. 32 which had been isolated 12 months earlier. The organism was grown in digest broth for 24 hours before use and then diluted 10^{-3} or 10^{-4} in broth. Estimation of the number of organisms present by the technique of Miles and Misra (1938) gave viable counts of 10,000 organisms at 10^{-4}. When 0.04 ml. of a 10^{-4} dilution (500 organisms) was injected, it was found that about 60 to 70 per cent. of controls were infected. One hundred per cent. of infections could be produced by 0.02 ml. of a 10^{-3} dilution, *i.e.*, 2,000 organisms.

The virulence of the infections produced is shown by their rapid progress in all the control cases. There was no sign of spontaneous resolution.

Further, in ten untreated animals, nine gave positive cultures of *Ps. pyocyanea*, and one a mixed growth of *Ps. pyocyanea* and *Staph. albus.*

Experiments.—These were divided into two groups: in Group I the effect of an immediate subconjunctival injection of polymyxin on the prevention of infection was investigated, and in Group II treatment was not started until there was already an established lesion.

Group I. Immediate Treatment

Preliminary Trial.—The right corneae of four rabbits were infected with *Ps. pyocyanea* (500 organisms in 0.04 ml.). Two, untreated, developed severe infection, and within 48 hours the whole cornea was involved. These two rabbits were killed, and culture of the corneae revealed a profuse growth of *Ps. pyocyanea.*

The two remaining animals received 500,000 units of polymyxin E subconjunctivally within 30 minutes of the infecting intra-corneal injection of *Ps. pyocyanea*; the same dose was given 24 hours later, and again 24 hours after that. After the first 24 hours moderate corneal oedema developed in both cases but this disappeared within 7 days. There was no sign of infection in either instance. Faint nebulae along the needle tracks were all that remained.

Series 1.—The right corneae of seven rabbits were injected with *Ps. pyocyanea* (500 organisms in 0.04 ml.), and three were kept as controls.

In all three controls corneal infiltration rapidly progressed and there was advanced infection after 48 hours. In one the whole cornea was involved after 72 hours and the rabbit was killed. Culture revealed a heavy growth of *Ps. pyocyanea.* The two other controls also showed marked and increasing infiltration after 48 hours and each was given 500,000 units of polymyxin subconjunctivally. This was done as a preliminary trial for the delayed treatment series to follow. In both, infiltration was very advanced

at the time of injection, but 24 hours later there was less discharge and there had been no further extension of the lesion. There was, however, marked ulceration and the rabbits were destroyed.

The cases treated immediately received 500,000 units of polymyxin E subconjunctivally within 30 minutes of the intra-corneal injection of *Ps. pyocyanea*. To three of the rabbits a further 500,000 units were given on the 2 subsequent days and 250,000 on the fourth day. Moderate corneal haze developed in all, but there was no sign of infection. After 14 days two showed very faint corneal nebulae while in the third the nebula was more marked and there was slight corneal vascularization.

In the fourth instance 500,000 units were given on the first 3 days but on the fourth day the rabbit appeared very weak and was destroyed. The cornea appeared free from infection. It was cultured and there was no growth. One other rabbit in this series became weak and ataxic on the fourth day but rapidly recovered. It is probable that this was a toxic manifestation and this is discussed below.

Series 2.—The right corneae of five rabbits were infected with *Ps. pyocyanea* (500 organisms in 0.04 ml.). One remained as control and developed a rapidly extending infection, the whole cornea being involved in 72 hours. Culture revealed *Ps. pyocyanea* in large quantity.

The four remaining animals each received 200,000 units of polymyxin subconjunctivally within 30 minutes of the initial infection and then further doses at 24-hour intervals. A very slight corneal haze developed in all cases but there was no sign of infection. All that remained after 10 days was very slight nebula formation at the position of the needle puncture in the cornea.

Series 3.—The right corneae of eight rabbits were infected (500 organisms in 0.04 ml.). Two served as controls, and the treatment given to the remaining six was as in Series 2. Again the controls rapidly became infected while all the treated animals remained free from infection.

This series was photographed at intervals. A typical case is shown in Figs 3–6. Figs 1 and 2 show a control rabbit at 24 and 48 hours. The rapid progress of the infection is clearly shown.

Thus, in Group I, all six control rabbits became rapidly infected while the fourteen which received prophylactic polymyxin were protected in every instance.

Group II. Delayed Treatment

Series 1.—The right corneae of seven rabbits were infected with *Ps. pyocyanea* (500 organisms in 0.04 ml.) but three did not develop infection. The remainder developed marked ulceration.

Of the four which became infected, one was left as a control and ulceration proceeded rapidly, the whole cornea becoming involved in 48 hours. The animal was killed, and culture of cornea showed a heavy growth of *Ps. pyocyanea*.

After 24 hours the three other cases showed infiltration with ulcers 6 to 7 mm. in diameter, and 330,000 units of polymxyin were given.

Two received a total of four injections at daily intervals after which time, as infection appeared to be overcome, treatment was stopped. There was no recurrence and the eyes settled down and became entirely quiet in 10 to 12 days. Moderate nebulae with slight vascularization remained after 28 days.

The third treated case had a 3-mm. hypopyon after 4 days' treatment, but, as the ulcer was improving, treatment was continued for a further 2 days, when the hypopyon disappeared and the cornea healed. A dense nebula resulted but the eye became quiet.

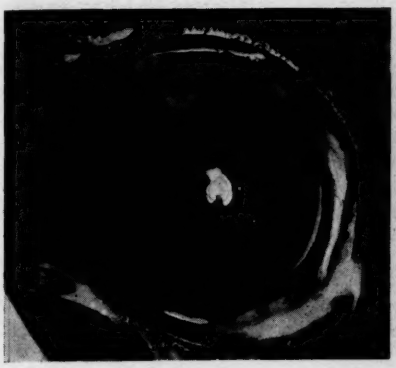


FIG. 1.—Control case. Ulcer on day after infecting dose.

FIG. 2.—Same control case one day later. Note discharge and involvement of whole cornea.

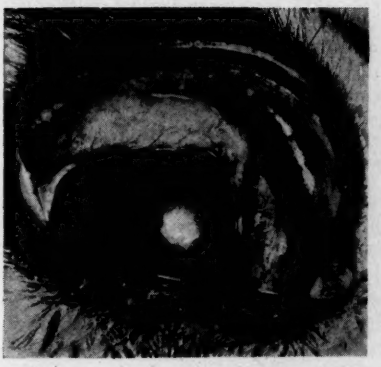


FIG. 3.—Appearance of a case in immediate treatment series on day after infecting dose. No discharge—moderate corneal oedema.

FIG. 4.—Same case one day later.

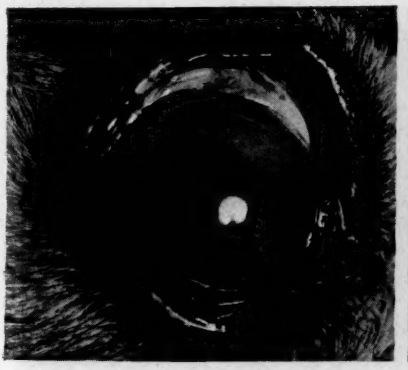


FIG. 5.—Same case 6 days after initial injection.

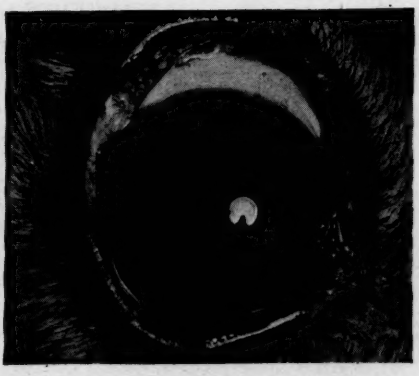


FIG. 6.—Same case 9 days after initial injection.

(All six photographed cases in this series gave identical results.)

Series 2.—The right corneae of eight rabbits were infected, 2,000 organisms in 0.02 ml. being given. Ulcers varying from 4 to 7 mm. in diameter were obtained after 24 hours. Treatment was started in six cases and two were left as controls.

In the controls infiltration spread rapidly during the next day, and the rabbits were killed. Culture of the corneae revealed *Ps. pyocyanea*.

The six cases treated each received 330,000 units of polymyxin E subconjunctivally for 6 days and 150,000 units on the seventh. In three instances infiltration rapidly decreased and after 15 days slightly vascularized nebulae were all that remained.

In the fourth case the cornea healed well but the rabbit died on the 12th day, when treatment had already been stopped for 5 days. Culture of the cornea revealed no *Ps. pyocyanea* but a few colonies of *B. coli*.

In the two remaining cases, moderate infiltration was still visible on the 11th day, and in one, definite discharge had restarted. Both animals were killed; in the case with discharge the corneal culture grew *Ps. pyocyanea*, but in the other culture only a few colonies of staphylococci were found.

Series 3.—Eight corneae were injected (2,000 organisms in 0.02 ml.) and 24 hours later all were found to be infected. In two rabbits left as controls, infection advanced rapidly, and they were both killed after 48 hours. The six treated rabbits all received 330,000 units of polymyxin E for 4 days, followed by 200,000 units for 2 days. Photographs were taken of this series, a typical result being shown in Figs. 7–12.

The infection was overcome in all the treated animals in this series. In five the recovery was uneventful, and after 10 days the eyes appeared quiet though there were dense nebulae. The sixth rabbit died from intercurrent infection on the 8th day (two days after cessation of treatment). The cornea was excised and cultured but no *Ps. pyocyanea* was found. Clinically the ulceration appeared to be entirely overcome.

Series 4.—The right corneae of seven rabbits were infected with *Ps. pyocyanea*. On the next day corneal ulceration and infiltration had occurred in every case.

The rabbit showing the least infiltration was left as a control, and the remaining six had surface cultures taken. In one case there was no growth but in the other five *Ps. pyocyanea* was grown. Polymyxin (100,000 units) was given 24 hours after the initial infection and at this time the corneal infiltration varied from 3 to 6 mm. in diameter.

Treatment was continued, giving 100,000 units of polymyxin subconjunctivally each day. After 48 hours of treatment surface cultures were clear in every case, even though there was still marked infiltration. After 72 hours five of the rabbits were progressing satisfactorily, but in one there was still considerable ulceration and the animal was killed. Culture from the excised cornea, however, revealed no *Ps. pyocyanea*. In the remaining five animals, treatment was continued daily for a total of 6 days. After 96 hours all the surface cultures were still free from *Ps. pyocyanea*, though one gave a moderate growth of *Staph. aureus*, and one a profuse growth of diphtheroids.

In four instances uneventful healing occurred, leaving small nebulae moderately vascularized. The remaining case appeared free from infection on the 11th day but the nebula was bulging slightly and the rabbit was killed. The cornea was excised and found to be thinned in the centre. It seemed to be free from infection and culture gave no growth.

In the control rabbit infection had spread rapidly and the animal was killed after 48 hours. Culture gave a profuse growth of *Ps. pyocyanea*.

In Group II, therefore, the ulceration was entirely overcome in fifteen (71 per cent.) of the 21 cases treated. There was a marked improvement in five instances (24 per cent.), and in these, although some infiltration and ulceration remained, culture of the excised corneae in no case revealed

FIG. 7.—Cornea on day after intra-corneal injection of *Ps. pyocyanea.* Treatment with subconjunctival polymyxin was started immediately after this photograph was taken.

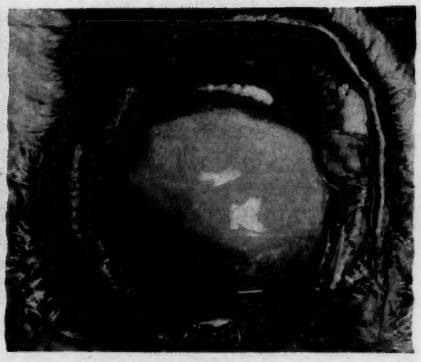


FIG. 8.—Same cornea 2 days later. Note absence of discharge.

FIG. 9.—Same cornea on seventh and last day of treatment. Infiltration and oedema still present.

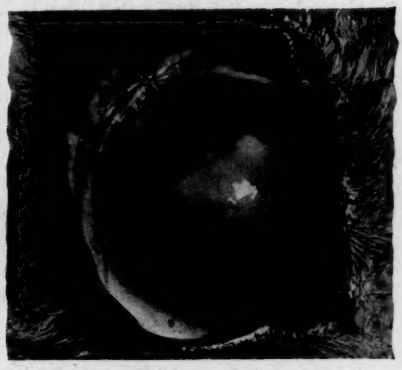


FIG. 10.—Same cornea 14 days after initial injection. Firm nebula forming—vascularization commencing.

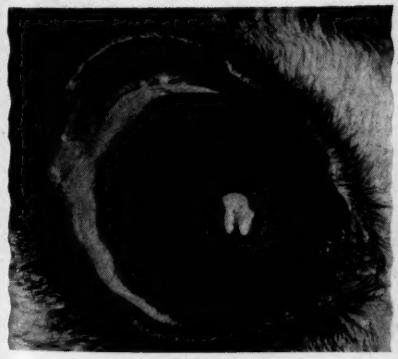


FIG. 11.—Same cornea on 21st day.

FIG. 12.—Same cornea seventh week. Eye quiet. Firm nebula—superficial vascularization has shown no change for two weeks.

Typical example of a successfully treated case.

Ps. pyocyanea. The rabbit which died only 2 days after the cessation of treatment has been included here, since there was still a possibility of recurrence, although the corneal infection appeared to have been overcome.

In the remaining case the infection was delayed but was not overcome, and culture of the excised cornea revealed *Ps. pyocyanea.* In every instance there was an infection of considerable severity before treatment was started.

Clinical Use of Polymyxin

We have had the opportunity of trying the subconjunctival injection of polymyxin clinically in only two cases. In these, no untoward local or systemic reaction occurred even though daily injection of 200,000 units was given for 5 days.

The injection, if made with mydricaine as the solvent for the polymyxin, is not painful, though a varying amount of aching is to be expected, starting after half an hour and lasting for about 45 minutes.

(1) One case when seen had already had penicillin and was having streptomycin but the ulceration and hypopyon were still increasing. The ulceration had followed a corneal foreign body. The clinical appearance was that of a *Ps. pyocyanea* ulcer but a surface culture did not give a growth.

The subconjunctival injection of 200,000 units of polymyxin led to the disappearance of the hypopyon within 2 days and rapid improvement. After 21 days, however, there was an increase of corneal infiltration, the eye again became irritable, and the hypopyon recurred. Subconjunctival polymyxin (200,000 units daily) was again given and within 2 days the hypopyon had gone and the corneal infiltration was much improved. Injections were continued for a further 3 days and recovery was uneventful.

(2) In the second case marked endophthalmitis was already present when first seen and culture revealed *Bacillus coli.* Polymyxin (200,000 units) were given daily for 3 days. The eye quietened but too much disorganization had occurred to give hope of useful vision and the eye became soft.

Discussion

Polymyxin can be injected subconjunctivally in doses sufficient to allow therapeutic amounts to penetrate the globe without causing any serious local toxic effects.

In the case of two rabbits given 500,000 units of polymyxin subconjunctivally (Group I, Series 1), weakening of the legs, particularly the hind legs, developed. There is little doubt that this was a manifestation of the neurotoxic effect of polymyxin E, but there was no other instance of this symptom where smaller and apparently adequate doses were used.

Further, a dose of 500,000 units in a rabbit corresponds to a systemic dose of 250,000 units per kg. bodyweight, whereas a similar injection in man would correspond only to about 10,000 units per kg., which is approximately the recommended systemic dose. Ten thousand units (1 mg.) of polymyxin E

per kg. bodyweight have been administered 4-hourly to human subjects for as long as 2 weeks without apparent toxic effect (Swift and Bushby, 1951). It appears from our experimental findings that, so far as corneal infections are concerned, it is unnecessary to give a dose as large as 500,000 units. This is, in fact, inadvisable as it leads to greater corneal oedema than does a smaller dose.

The experimental results suggest that polymyxin should overcome corneal infections with *Ps. pyocyanea* in man in a high proportion of cases if the infections are seen and diagnosed early. We are anxious to obtain such cases for treatment.

Ps. pyocyanea was chosen as the infective organism in these experiments since it is particularly resistant to treatment by other means. It is probable that polymyxin would be at least equally effective against infection with other Gram-negative organisms.

SUMMARY*

(1) Polymyxin E is highly soluble in water. It is relatively non-irritant and therefore suitable for subconjunctival injection.

(2) In the rabbit an injection of 250,000 units of polymyxin subconjunctivally led to therapeutic levels in the cornea, aqueous, and vitreous after 1 hour.

(3) Intracorneal injection of *Ps. pyocyanea* failed to produce infection in fourteen rabbits given subconjunctival polymyxin E immediately after the infecting dose. Rapidly extending infection developed in six control rabbits.

(4) Twenty animals with experimentally produced *Ps. pyocyanea* ulcers were treated with subconjunctival polymyxin E. Infection was overcome in all but one case. In the six untreated controls infection spread rapidly.

(5) No proven cases of pyocyaneous corneal ulcers have been treated clinically. Subconjunctival injections of 200,000 units of polymyxin have been given to adults without untoward effects. In the two treated cases of corneal ulceration of which we have experience the results were encouraging.

We are greatly indebted to Mr. J. Edwards of the Research Department of the Institute of Ophthalmology for his technical assistance, and to Dr. Peter Hansell and his staff in the Photographic Department for their co-operation.

The polymyxin E was kindly supplied by Burroughs Wellcome Ltd., to whom our thanks are due for their advice.

REFERENCES

BIGNELL, J. L. (1951). *British Journal of Ophthalmology*, **35**, 419.
BROWNLEE, G., and BUSHBY, S. R. M. (1948). *Lancet*, **1**, 127.
——— ——— and SHORT, E. I. (1949). *Ann. N.Y. Acad. Sci.*, **51**, 952.
FLEMING, A., and SMITH, C. (1947). *Lancet*, **1**, 401.
JACKSON, D. M., LOWBURY, E. J. L., and TOPLEY, E. (1951). *Ibid.*, **2**, 137.
LANGHAM, M. (1951). *British Journal of Ophthalmology*, **35**, 614.
MAY, J. R., VOUREKA, A. E., and FLEMING, A. (1947). *Brit. med. J.*, **1**, 627.
MILES, A. A., and MISRA, S. S. (1938). *J. Hyg., Camb.*, **38**, 732.
SORSBY, A., UNGAR, J., and BAILEY, N. L. (1952). *Brit. med. J.*, **1**, 119.
STANSLY, P. G., SHEPHERD, R. G., and WHITE, H. J. (1947). *Bull. Johns Hopk. Hosp.*, **81**, 43.
SWIFT, P. N., and BUSHBY, S. R. M. (1951). *Lancet*, **2**, 183.

* Since this article was written a few cases of *Ps. pyocyanea* corneal infection in humans have been treated with polymyxin, and the results have been promising.

Brit. J. Ophthal. (1952) 36, 362.

OPERATIVE TREATMENT OF CONGENITAL PTOSIS*

REPORT ON 25 OPERATIONS

BY

G. I. SCOTT

Edinburgh

IF one excludes excision of skin, or of portions of the orbicularis, from the upper lid, operations for the relief of congenital ptosis may be divided into three groups:

(*i*) those designed to make the frontalis raise the upper lid,
(*ii*) those making use of the superior rectus,
(*iii*) those designed to shorten and advance the levator palpebrae muscle.

As Berke has pointed out, however, more than eighty operations have been described, although all are modifications of one or other of the above procedures. This multiplicity of methods is proof in itself that surgeons, in general, do not obtain consistently good results from any one operation.

Since Dransart (1880) first suggested the insertion of subcutaneous sutures of catgut to try to create a band of cicatricial tissue between the frontalis and the upper lid, many similar procedures have been described, but to-day the most frequent method of utilizing the frontalis is undoubtedly by the insertion of strips of fascia lata, as suggested by Wright (1922) and recommended by Lexer (1923) and other authors. This operation is widely used and is an effective method of correcting many cases of ptosis. It has, however, the undoubted disadvantage that the cosmetic result is often not satisfactory, which is hardly surprising in view of the fact that the pull is vertically upwards with consequent loss of the normal curvature of the upper lid. Even the insertion of extra stitches to join the fascia to the skin, as suggested by Juler (1939), does not achieve a good cosmetic result in most cases. It is of interest to note that Juler himself, although mentioning the latter procedure, expressed a preference for the method of Blaskovics (1929), namely advancement and resection of the levator, to that described by Wright and by Lexer.

The use of the superior rectus (as originally suggested by Parinaud (1897) and Motais (1897), with modifications introduced by later workers) while it produces, when successfully performed, a good cosmetic result, is not without grave disadvantages. A certain degree of lagophthalmos is unavoidable since the eyeball cannot roll upwards during sleep and there is consequent danger of exposure keratitis in cases where ptosis is fully corrected by this method. It is also difficult to avoid undue arching of the lid margin, and

* Received for publication March 3, 1952.

there is a definite danger, in cases of unilateral ptosis, of producing post-operative vertical muscle imbalance.

The third basic procedure, namely to shorten and advance the levator palpebrae muscle, was first suggested by Bowman (1857) in a report of one case. Following this, various approaches to the levator were described by Wolff (1896), Eversbusch (1883), Blaskovics (1929), and other writers.

The Eversbusch procedure consisted of a shortening of the levator by taking a tuck in it, the approach being through the skin of the upper lid. While this operation has proved effective in cases of ptosis of slight degree, it is generally regarded as ineffective in severe cases.

Blaskovics (1908) described an operation for resection of the levator using a conjunctival approach as had been suggested by Bowman fifty years before, but his technique was not fully elaborated until 1929. In 1923 he reported his results in 21 operations after resection of a portion of the levator and excision of a considerable portion of the tarsus. Six years later he elaborated his technique, by the addition of extra sutures designed to create a fold in the upper lid, to improve the cosmetic result, and he recorded another twelve successful cases. In these 33 cases Blaskovics had only two over-corrections and one under-correction.

Dunnington (1941), Malbran (1941), and other writers, although advocating the Blaskovics type of operation as the best in selected cases, consider that the operation can be used successfully only when the levator muscle is present and active, and that there is a tendency to under-correction. On the other hand, the same writers stress that the operation has several great advantages in that lagophthalmos is rare, the margin of the lid is rarely deformed, and there is no wrinkling of the brow or backward tilt of the head, and no risk of producing diplopia.

While, as noted above, many surgeons consider that the levator must be active, if a resection type of operation is to give adequate correction, Blaskovics, and also Lindner (1934) and Jaensch (1935), all of whom published results showing a high proportion of successes, maintained that the operation could be used for correction of any degree of ptosis and even when the levator was apparently completely inactive.

More recently, Matthews (1949), as a result of considerable experience, has expressed the opinion :

> for congenital ptosis, shortening and advancement of the levator muscle is the most satisfactory method of correction, even if no action of the muscle can be detected pre-operatively.

Before 1947 various operative procedures were used at the Royal Infirmary of Edinburgh, and during the years immediately prior to that date the method most commonly used was a Lexer type of operation. It is fair to state that no method appeared to produce anything like consistently good results. One conclusion I had come to, however, was that when successful the Blaskovics type of operation produced an excellent functional and cosmetic

result. It therefore seemed desirable to try to find out whether such failures as did occur were due to faults in the method as described by Blaskovics, or to faults in the performance of the operation.

ANATOMY.—Agatston (1924), in describing a modification of Blaskovics's operation stated that he was convinced that poor results were often due to faulty technique, and both Hildreth (1941) and Berke (1945) have stressed certain anatomical details which are essential to the proper performance of advancement and resection of the levator.

It is true that Wolff (1905) drew attention to the surgical importance of certain points in the anatomy of the region with which we have to deal, and in particular to the insertions and relations of the levator palpebrae superioris and of Muller's muscle. As Berke has pointed out, however, other surgeons, although they may have included both the levator and Muller's muscle in their resections, have failed to record any differentiation.

Many surgeons have described the levator as sometimes very friable and even as absent, an observation which makes one think that on some occasions they may have mistaken Muller's muscle for the levator, and advanced and resected the former in mistake for the latter. In the author's experience, Muller's muscle, although usually thin and friable, can often be dissected quite readily as a separate layer, which one could well imagine a surgeon, unfamiliar with the operation, using in his resection and advancement. On the other hand, the aponeurosis of the levator is always considerably thicker and stronger and should certainly be capable of sufficient resection and advancement, if clearly exposed, to correct even severe degrees of ptosis.

Matthews (1949) has also stressed how bulky the levator is, even when clinically there appears to be no levator action at all.

Whitnall (1921) has given us a detailed description of the insertion of both the levator palpebrae superioris and of Muller's muscle, and, as has been noted above, the recent anatomical studies of both Hildreth and Berke have emphasized their surgical importance.

As Whitnall has said, the levator terminates in an expanded tendon called the " aponeurosis ", and the fore edge of this breaks up into fine connective tissue fibres which are inserted into the skin of the lid and the lower third of the anterior surface of the tarsus.

Moreover, lying in close contact beneath the aponeurosis is a thin lamella of pale, smooth muscle fibres, which appears to be a direct continuation of the fleshy belly, but is inserted directly into the upper margin of the tarsal plate. This is the superior palpebral involuntary ' muscle of Muller ', and constitutes a secondary insertion of the levator.

Whitnall also pointed out that the aponeurosis of the levator is a band of dense connective tissue about 7 mm. in depth from before backwards, and that it fans out into lateral and medial horns.

The principal insertion of the levator, therefore, is into the skin of the whole pre-tarsal portion of the lid, the uppermost fibres fusing with the septum orbitale, and the lowermost fibres gaining attachment to the lower third of the anterior surface of the tarsal plate (Fig. 1, opposite).

Of the two ' horns ' the lateral is the stronger. On the medial side the aponeurosis becomes less well-defined as it thins out to gain attachment to bone along with the medial palpebral ligament.

As described by Whitnall, Muller's muscle forms a thin sheet of red muscle fibres lying in front of the conjunctiva, and connected to the upper border of the tarsal plate, the muscle being about 1 cm. in length.

In addition, some authors point out yet another attachment of the levator, to the conjunctiva of the upper fornix of the conjunctiva. Whitnall states that this attachment is in reality a thickening of the muscle sheaths: nevertheless it is an attachment which has to be freed at operation.

Another point of some practical importance is the fascial sheath of the levator. Once again we are indebted to Whitnall for an adequate description of this structure:

Its superficial part, covering the upper aspect of the muscle just behind the aponeurosis, is condensed to form a definite ligamentous band, which stretches transversely across to reach the orbital walls on either side, parallel with but attached at a higher level than the aponeurosis: medially the main connection is to the trochlea, but behind this some fibres pass to the bone, and a well-marked slip passes forward to bridge the supra-orbital notch; laterally the band is connected with the stroma of the lacrimal gland and cuts into it, as does the lateral horn of the aponeurosis, and beyond the gland it reaches the lateral orbital margin: it lies for the most part free above the aponeurosis, but stout strands of connective tissue may unite them. In front of this ligamentous condensation the sheath becomes abruptly so thin that it appears to end in a free border.

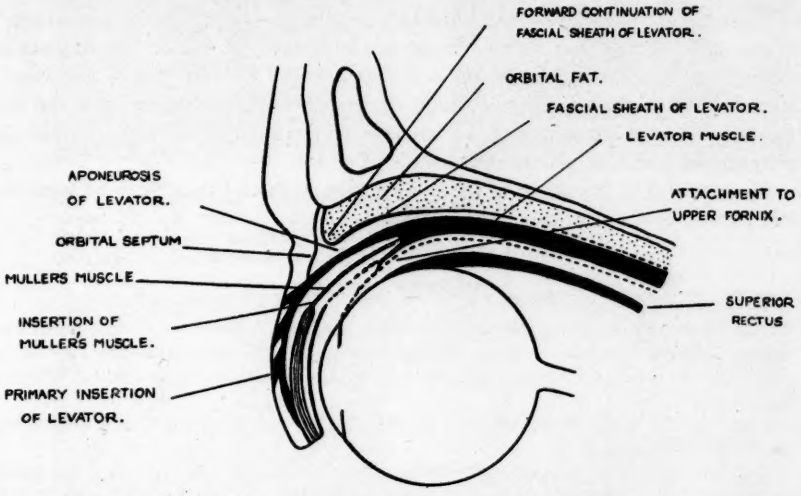


FIG. 1.—Relationships of structures involved in operation for resection and advancement of levator and Muller's muscle (after Whitnall, 1921).

APPLIED ANATOMY.—In the light of these observations, Blaskovics's operation was performed upon fairly fresh cadavers, and an attempt was made to correlate the findings with those found at operation upon the living subject.

In the cadaver the plane of cleavage between the levator and Muller's muscle was difficult to define, mainly owing to the relative similarity in colour of the bloodless tissues and also to the hardening of them by preservative fluids.

During operations upon the living subject, a good deal of variation was found. On reflection of the conjunctiva, first by sharp dissection and then by 'scissor-spreading', Muller's muscle was always readily identified as a thin red sheet of muscle fibres, and, if this was picked up by traction sutures, the line of cleavage between the muscle and the aponeurosis of the levator could be readily identified in view of the contrasting pale pink aponeurotic appearance of the connective-tissue of the levator, which was always quite a substantial layer of tissue.

There was also considerable variation in the friability of Muller's muscle. In some cases the muscle was readily dissected as quite a well-defined layer which one might easily have resected and advanced in mistake for the levator: in others it was much more friable.

The fascial sheath of the levator also presented some differences of practical importance. In the cadaver, the anterior portion of the sheath, anterior that is to the ligamentous condensation described by Whitnall, was very thin and friable. In the living subject, one could, however, quite readily dissect along the upper surface of the levator aponeurosis and beneath the anterior portion of the fascial sheath (Fig. 1), and it is this plane of cleavage which one should define in order to avoid prolapse of orbital fat. Only occasionally did the sheath tear during dissection, and then only slightly.

Dissection in the above planes, first between the conjunctiva below and Muller's muscle above, and then along the upper surface of the levator but beneath its fascial sheath, allows of dissection as far back as the anterior part of the belly of the levator. In this way approximately 10 mm. of the levator are exposed, and this, together with the 8 mm. which can be removed from the tarsal plate, is ample for purposes of resection and advancement.

If one wishes to free more of the levator, then its fascial sheath can be separated still further by " scissor-spreading " dissection.

Operative Technique

Bearing the above anatomical points in mind, seventeen consecutive cases of ptosis were operated upon by a modification of Blaskovics's original technique. Sixteen of the cases were congenital in nature, and one was an adult case of acquired ptosis following encephalitis.

Eight of the cases were bilateral, so that in fact 25 consecutive operations were performed.

It is of interest to note that the method employed since 1947 has been essentially similar to that adopted by Matthews in the same year, and described by him in 1949. In some respects, however, for reasons which will be discussed later, the technique, particularly in the later stages, is different.

The various stages in the operative procedure, emphasizing the application of the anatomical details referred to above, may be summarized as follows:

(*i*) The first stage, after double-eversion of the upper lid, is the insertion of three traction sutures in the upper border of the tarsal plate. The conjunctiva is then incised 2 mm. from the upper edge of the tarsus (Fig. 2, opposite).

The conjunctiva is now dissected downwards, partly by cutting but mainly by ' scissor-spreading' (Fig. 3), thus exposing the under surface of Muller's muscle and its insertion into the tarsal plate. The three double-armed sutures (No. 1 black silk) to be used later in the advancement of the levator are then inserted in the conjunctiva, as originally described by Blaskovics.

(*ii*) It is to be noted that Muller's muscle covers the whole of the doubly-everted tarsal plate, whereas the levator aponeurosis—covered by Muller's muscle—only overlies the lower third of the tarsal plate. A spatula should therefore be inserted behind the doubly-everted upper lid, so as to push forwards the anterior portion of the levator aponeurosis. Three traction sutures (No. 1 white silk), taking a deepish bite, are now inserted immediately below the lower border of the tarsal plate so as to pick up both Muller's muscle and the underlying aponeurosis of the levator (Fig. 4). The spatula is then removed.

(*iii*) As soon as traction is applied, the next step should be to dissect backwards along the under surface of Muller's muscle. The line of cleavage is exposed by snips with scissors, and the latter are then inserted and ' spread ' (Fig. 5). In this way a free space is cleared reaching as far back as the under surface of the belly of the levator. During this procedure the fibres going to the upper fornix of the conjunctiva will also be divided (Fig. 6, overleaf).

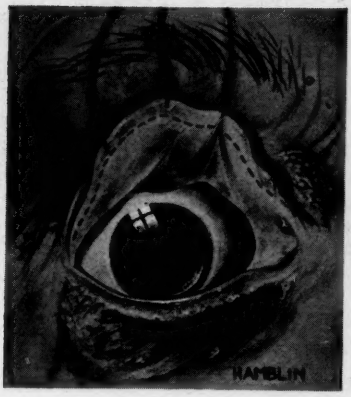


FIG. 2.—Control of doubly-everted upper lid by traction sutures. The dotted line shows the position of the incision into the conjunctiva.

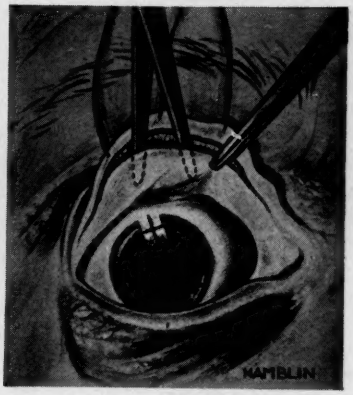


FIG. 3.—Separation of conjunctiva from underlying Muller's muscle by 'scissor-spreading' dissection.

FIG. 4.—Three black double-armed sutures, to be used later in advancement of levator, inserted in conjunctival flap retracted downwards. White traction sutures have been inserted immediately below the lower border of the tarsal plate to pick up both Muller's muscle and the underlying aponeurosis of the levator.

FIG. 5.—Exposure of line of cleavage between conjunctiva below and Muller's muscle and levator above by 'scissor-spreading' dissection.

(*iv*) The next stage is dissection anterior to the traction sutures. Muller's muscle and the fibres of the levator attached to the lower third of the tarsus must be stripped from the tarsal plate to expose the portion of the aponeurosis immediately posterior to the fusion of the orbital septum with the latter.

Dissection should then be continued so as to cut through the levator aponeurosis just behind the orbital septum and thus reach the upper surface of the levator (*see* Fig. 1).

By 'scissor-spreading' one then clears a plane of cleavage between the upper surface of the levator and the anterior part of its fascial sheath. Again, once the initial cuts have been made to expose the line of cleavage, free exposure is best achieved by 'scissor-spreading' (Fig. 7, overleaf).

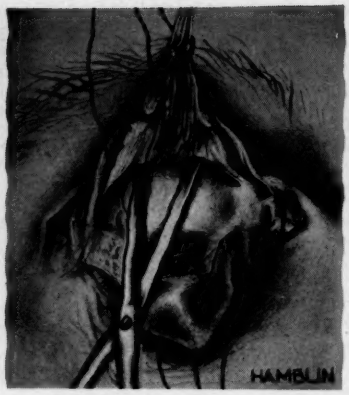


FIG. 6.—Further dissection to reach under-surface of belly of levator.

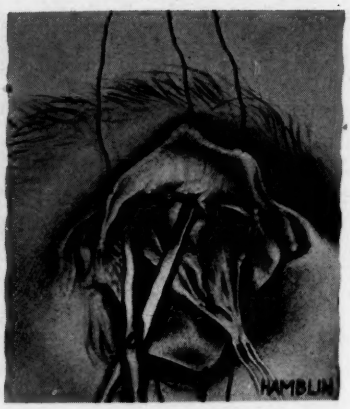


FIG. 7.—Levator and Muller's muscle retracted downwards. Dissection along upper surface of levator by cutting and 'scissor-spreading'.

FIG. 8.—Insertion of 'fold' sutures.

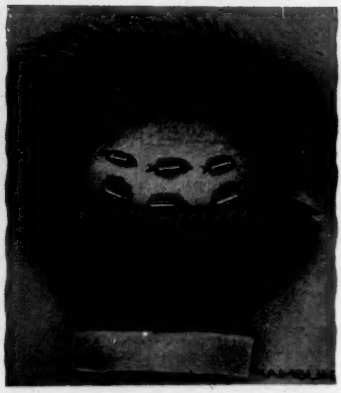


FIG. 9.—Levator sutures left long and strapped down on to cheek.

The 'hanging curtain' of the orbital septum is thus left attached to the skin through the terminal fibres of the levator aponeurosis, so that, when the anterior edge of the shortened levator is ultimately stitched to the anterior surface of the tarsus, the orbital septum will once more fall into place.

The sutures originally inserted into the conjunctiva are now passed through the levator, on an average about 10 mm. behind the traction sutures, in the manner described by Blaskovics, and the excess levator (with the underlying Muller's muscle) is excised.

(*vi*) The next step is to excise a portion of the tarsal plate, and my usual practice, in cases where the ptosis is moderately severe, is to leave 2–3 mm. of plate in the infant and 3–4 mm. in the adult. In less severe cases one should leave rather more of the tarsal plate, but excise the same amount of levator. In cases of complete ptosis, the extra effect should be obtained by resecting more of the levator.

(*vii*) The sutures used in the resection of the levator are then inserted between the anterior surface of the tarsus and the skin, so as to emerge on the skin-surface 2–3 mm. above the lid-margin. In this way the shortened levator is now once more re-attached to the skin and also becomes adherent to the anterior surface of the remaining tarsal plate.

(*viii*) With regard to the ' fold-forming sutures ', I have found the method recommended by *Spaeth (1939) more effective than* Blaskovics's original suggestion. Three double-armed sutures (No. 00 black silk) are therefore inserted through the upper fornix to emerge on the skin-surface 4–6 mm. above the lid-margin (Fig. 8).

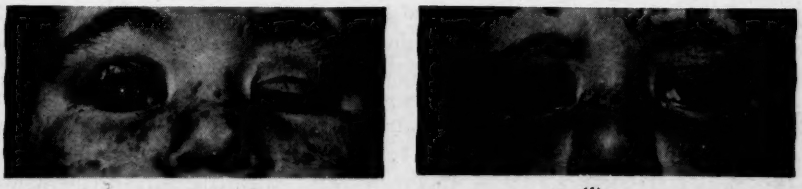
All sutures are tied over small glass beads or pieces of plastic tubing. The levator stitches are left long and fastened down on the cheek (Fig. 9). A pad and bandage are then applied, and an injection of 1,000,000 units penicillin is given intramuscularly.

Post-operative Care.—*The sutures are cut short in 24 hrs, since post-operative oedema* usually suffices to provide enough closure of the palpebral aperture to prevent any damage *from exposure keratitis. The cornea is kept covered by a film of sodium sulphacetamide* or penicillin ointment, and at first the eye is usually kept covered at night as a precautionary *measure.* The sutures are removed on the 8th day.

Results

The results in 25 consecutive operations have been as follows:

(1) In twenty cases a perfect or a near-perfect result was obtained. The surgical result, in so far as the correction of the ptosis was concerned, was excellent in all of them.



(*a*) (*b*)

FIG. 10(*a*).—*Right eye* 10 days after operation. *Left eye* before operation.
FIG. 10(*b*).—*Right eye* 7 months after operation. Good correction of ptosis, but arching of lid-margin and a fold of redundant skin are seen. Imperfect cosmetic result. *Left eye* 5 months after operation. Perfect result.

An absolutely perfect cosmetic result (Fig. 10, left eye) is always difficult to attain, and was only achieved in eleven of these twenty cases. The other nine cases, classified as near-perfect, showed minor degrees of arching of the lid-margin (four cases), or trivial degrees of under-correction (three cases) or over-correction (two cases). The right eye in Fig. 10 was one of the poorest cosmetic results in the ' near-perfect ' group, the right eye in Fig. 11 being more typical of the slight imperfection which it is difficult to avoid. In none of these cases, however, was the residual defect sufficient to merit further operative interference, although, at a future date, the cosmetic effect might, in some cases (for example Fig. 10*b*, right eye) be improved by removal of redundant folds of skin.

The right eye in Fig. 12 is another example of a perfect result.

FIG. 11.—Case of moderate ptosis, right eye, 3 years after operation. ' Near-perfect ' result.

FIG. 12.—Case of moderate ptosis, right eye, 3 years after operation. Perfect result.

(2) In two cases of unilateral ptosis, there was a definite under-correction which will require a second operation to achieve a perfect result. It should also be noted, however, that in three of the twenty cases reported above a second operation was required before perfection was achieved, and there is no reason to suppose that a perfect or near-perfect result will not also be achieved in these two cases.

(3) In one case with unilateral ptosis and associated paralysis of the superior rectus an under-correction was purposely performed. The operation was effective in that the faulty posture which had occurred was corrected, although naturally the cosmetic result was not as good as one would like to have achieved.

(4) In one patient with bilateral ptosis and marked blepharophimosis the result has been poor, and further operations will undoubtedly be required to deal with this complicated case.

Conclusions

Only by attention to all the anatomical details described above can one hope to attain the maximum benefit from advancement and resection of the levator, and failure to observe some of these points may well account for the fact that, in general, surgeons do not appear to have achieved the results recorded by Blaskovics, Lindner, and Jaensch. It seems probable, however, that surgeons like Blaskovics, Lindner, and Jaensch certainly performed advancements and resections of both the levator and Muller's muscle, since one could hardly imagine them achieving such a high percentage of success, particularly in cases of severe ptosis, in any other way.

It is true that in young children it is often difficult to assess whether or not the levator has any activity. In the present series, the advancement and resection operation was performed on a number of children, in whom several observers were of the opinion that the levator showed no activity, and yet, following operation, it was evident that there was in fact some function remaining. In any event, however, the results, in this series, have been equally effective, whatever the degree of ptosis, even in patients who had apparently no levator function when examined before operation. These findings agree with those originally recorded by Blaskovics and more recently emphasized by Matthews.

In the writer's opinion, the function of the superior rectus should be the main factor governing one's choice of operation.

IF THE SUPERIOR RECTUS IS NOT PARALYSED, THEN ONE SHOULD, I THINK, UNDOUBTEDLY DO A RESECTION AND ADVANCEMENT OF THE LEVATOR.

If, however, the ptosis is complete or nearly so, there will be considerable folding of the skin of the upper lid after correction of the ptosis, and in such cases an elliptical portion of skin will require to be removed, preferably 6 months or so later, to achieve the best cosmetic effect.

In severe cases of ptosis, and especially in those complicated by blepharophimosis, it is, I think, probably wiser not to attempt to achieve a full correction of the ptosis at the first operation. A partial correction will go far to correct faulty posture, and will enable the child to see. A second operation can then be performed at a later date to achieve the full effect.

Moreover, even in cases of moderate severity, the first operation may, in some cases, result in a slight under-correction. It is probably wiser, therefore, to warn the parents, in all cases, that a second operation may be required to achieve the maximum functional and cosmetic benefit.

IF THE SUPERIOR RECTUS IS PARALYSED, THEN ONE IS LEFT, IT WOULD SEEM, WITH ONLY TWO RATIONAL ALTERNATIVES. If the frontalis is obviously active, a fascia lata graft operation, as described by Wright, Lexer, and others, may be performed. If, however, the frontalis is not active, one must, I think, be content with an incomplete correction of the ptosis, preferably by advancement and resection of the levator, so as to avoid the danger of over-correction and the possible occurrence of exposure keratitis. One can raise the lid so as almost to clear the pupil, but one should not attempt to obtain a perfect cosmetic result.

In my experience, marked weakness of the superior rectus is not common. It is often difficult to assess its function in young children, and eyes which were thought to have little or no upward movement, will often be seen to roll well upwards during sleep or under general anaesthesia. Since, in my view, the choice of operation should depend upon whether or not there is marked weakness of the superior rectus, careful and repeated examination should be made in all cases recorded as having marked weakness of upward movement.

To sum up, therefore, the operation of choice in cases of congenital ptosis should, in my opinion, be a resection and advancement of the levator palpebrae muscle, except perhaps in those cases which show associated paralysis of the superior rectus. The operation should, I think, be done when the child is 3 years old, although in very severe cases it may well be advisable to operate at an earlier date.

Summary

(1) The literature regarding the operative treatment of congenital ptosis is briefly reviewed.

(2) The applied anatomy governing the performance of resection and advancement of the levator palpebrae is discussed, and the operative technique is described in the light of these findings.

(3) A report is given of 25 consecutive operations for correction of ptosis.

In 20 cases a perfect or near-perfect result was obtained.

In two cases there was definite under-correction which will require a second operation, but there is no reason to suppose that a perfect or near-perfect result will not be achieved.

In one case, with associated paralysis of the superior rectus, an under-correction was purposely performed.

In one patient, with severe bilateral ptosis and marked blepharophimosis, the result has been poor, and further operations will undoubtedly be required.

(4) The choice of operation is discussed, and it is concluded that advancement and resection of the levator, by a modification of Blaskovics's original technique, should be the method of choice in most cases of congenital ptosis.

REFERENCES

AGATSTON, S. A. (1942). *Arch. Ophthal., Chicago*, **27**, 994.
BERKE, R. N. (1945). *Ibid.*, **33**, 269.
BLASKOVICS, L. DE (1908) *Szemészet, Budapest*, **45**, 196.
——— (1923). *Arch. Ophthal., Chicago*, **52**, 563.
——— (1929). *Ibid.*, **1**, 672.
BOWMAN, W. (1857). *Rep. roy. Lond. ophthal. Hosp.*, **1**, 34.
DRANSART (1880). *Ann. Oculist., Paris*, **84**, 88.
DUNNINGTON, J. H. (1941). *Med. Rec., Houston*, **35**, 880.
EVERSBUSCH, O. (1883). *Klin. Mbl. Augenheilk.*, **21**, 100.
HILDRETH, H. R. (1941). *Amer. J. Ophthal.*, **24**, 749.
JAENSCH, P. A. (1935). *Klin. Mbl. Augenheilk.*, **94**, 183.
JULER, F. A. (1939). *Trans. ophthal. Soc. U.K.*, **59**, 583.
LEXER, E. (1923). *Klin. Mbl. Augenheilk.*, **70**, 464.
LINDNER, K. (1934). *Ibid.*, **93**, 1.
MALBRAN, J. (1941). *Sem. méd., B. Aires*, **48** (2), 1456.
MATTHEWS, D. N. (1949). *Trans, ophthal. Soc. U.K.*, **69**, 179.
MOTAIS (1897). *Ann. Oculist., Paris*, **118**, 5.
PARINAUD, H. (1897). *Ibid.*, **118**, 12.
SPAETH, E. B. (1939). " Principles and Practice of Ophthalmic Surgery ", 1st ed., p. 320. Kimpton, London.
WHITNALL, S. E. (1921). " Anatomy of the Human Orbit and Accessory Organs of Vision ". Oxford Medical Publications, London.
WOLFF, H. (1896). *Arch. Augenheilk.*, **33**, 125.
——— (1905). *Z.-Augenheilk.*, **13**, 440.
WRIGHT, W. W. (1922). *Arch. Ophthal., Chicago*, **51**, 99.

Brit. J. Ophthal. (1952) 36, 373.

EFFECT OF CORTISONE ON RHEUMATOID NODULES OF THE SCLERA (SCLEROMALACIA PERFORANS)*†

BY

NORMAN ASHTON AND H. E. HOBBS

From the Department of Pathology, Institute of Ophthalmology, and the Royal Free Hospital, London

VAN DER HOEVE (1931), basing his observations on two cases, drew attention to a condition characterized by the spontaneous appearance of scleral perforations, which he named *scleromalacia perforans*. A somewhat similar case had previously been described by Holthouse (1893), and Kuhnt (1912) reported a case of scleral perforation associated with hydroa vacciniforme. Under the term *scleritis necroticans* Rochat (1933) described two further cases but he was later willing to accept the earlier designation. Van der Hoeve (1934) reviewed his original material with that of Rochat and referred to two additional cases. He noted that the disease was bilateral in most patients and began in the anterior sclera with yellow or greyish subconjunctival nodules, associated with a gradually developing scleral necrosis, progressing to perforation with exposure of the uvea. Three of these cases presented a history of pre-existing chronic articular disease of an ankylosing type and this feature he associated with the ocular condition to form a distinct syndrome. Following upon van der Hoeve's recognition of this disease-entity, further cases were reported by Eber (1934), Wojno (1935), Kiehle (1937), Cast (1937), Soriano and Riva (1937), and Urrets Zavalia and others (1937).

Verhoeff and King (1938) reviewed fourteen cases which they had at that time been able to trace in the literature and described a fifteenth in which the eye had been enucleated, thus providing the first complete histological report of the condition. They were able to confirm the features of the ocular manifestations as originally described and emphasized the association with rheumatoid arthritis. They were the first to point out that the histological changes in the scleral nodules were essentially similar to those of the subcutaneous nodules of rheumatoid arthritis, and they suggested that the reaction might be due to the deposition of a chemical substance arising in the course of some metabolic disturbance; the deposition of urates in gout was an analogous process. Indeed it is interesting to note that more recently van der Hoeve (1948) has advanced the theory that scleromalacia perforans arises from a disturbance of the lipoid and cholesterol metabolism, and that he associates it with the group of diseases which includes Hand-Schüller-Christian disease, Niemann-Pick disease, Tay-Sachs disease, and xanthomatosis.

* Received for publication March 4, 1952.

† Dedicated to Professor Lindner on the occasion of his 70th birthday.

Since the report of Verhoeff and King (1938), numerous cases, reviewed by François (1951), have been added to the literature, and it has become apparent, as pointed out by Franceschetti and Bischler (1950) and by Malbrán and Manzitti (1951), that there is a danger of confusing scleromalacia perforans with a number of other conditions, which are essentially different although clinically similar in some respects. However, in typical cases of scleromalacia perforans there is clearly an aetiological relationship between the scleral lesions and the co-existing rheumatoid arthritis, and we are in agreement with those who believe that, until the exact cause of the condition is known, it is more appropriate to regard scleromalacia as a manifestation of rheumatoid arthritis, thus belonging to the group of collagen diseases. This term was originally proposed by Klemperer, Pollack, and Baehr (1942) to designate a number of acute and chronic maladies of unknown aetiology in which there are widespread alterations of connective tissue, particularly in the extra-cellular substance. The category includes rheumatic fever, rheumatoid arthritis, polyarteritis, acute lupus erythematosus, generalized scleroderma, and dermatomyositis. The fibrinoid collagen change which is such a striking feature of scleromalacia, is such as would be expected in a collagen disease affecting a tissue with such a high collagen content as the sclera. This point, together with further arguments for regarding the pathological changes in scleromalacia as identical to those arising in other tissues in the collagen diseases, has been particularly well presented by Christensen (1951), Stillerman (1951), and Swan (1951).

Although the inclusion of apparently unrelated disorders within the group of the collagen diseases does not necessarily imply an aetiological relationship between them, their development is believed to be connected with immune processes and the noxious effects of hypersensitivity. The beneficial effects of ACTH and cortisone in such states have been amply demonstrated, and it appears that they may control the disease process by suppressing the inflammatory reaction resulting from antigen-antibody union in the tissues (Dougherty, 1951). On the other hand, Klemperer (1950) has suggested that there may be a primary abnormality in the chemical constitution of the ground substance, and since we now know that the formation of collagenous tissue and ground substance is to some extent subject to the influence of the adrenal cortex and other hormones (Russell, 1950), it is reasonable to suppose that disease in this system might arise from hormonal imbalances, which ACTH or cortisone therapy is able to rectify. Whatever the mode of action of such treatment, it would obviously be of interest to determine its effect upon the course of scleromalacia perforans, and the purpose of this paper is to report the treatment of such a case with cortisone, the remarkable alterations in the ocular lesions being described in detail. The subsequent death of the patient by providing an eye for pathological examination permitted comparison of the histological appearances with those of eyes from other patients in whom such treatment had not been possible.

Case Report

History.—A male patient aged 41 years, suffering from advanced rheumatoid arthritis of some 8 years' duration, was first seen by one of us (H. E. H.) on March 14, 1950, at the request of Dr. E. T. D. Fletcher. At that time the condition of scleromalacia perforans was fully established in both eyes. A history of bilateral scleritis 9 months previously and of a very recent appearance of scleral perforations was later obtained from Mr. J. E. M. Ayoub, assistant ophthalmic surgeon to the London Hospital.

Examination.—A number of yellowish episcleral nodules, about 3-4 mm. in diameter, and scleral perforations covered by intact conjunctiva through which the bluish-black uvea could be seen bulging slightly, were present anteriorly in both eyes. In some of the perforations yellowish-white sloughs of scleral tissue were to be seen, but no indications of an inflammatory cause were present, the media being entirely clear. There was, however, slight conjunctival injection and photophobia. The appearance is shown in Fig. 1.

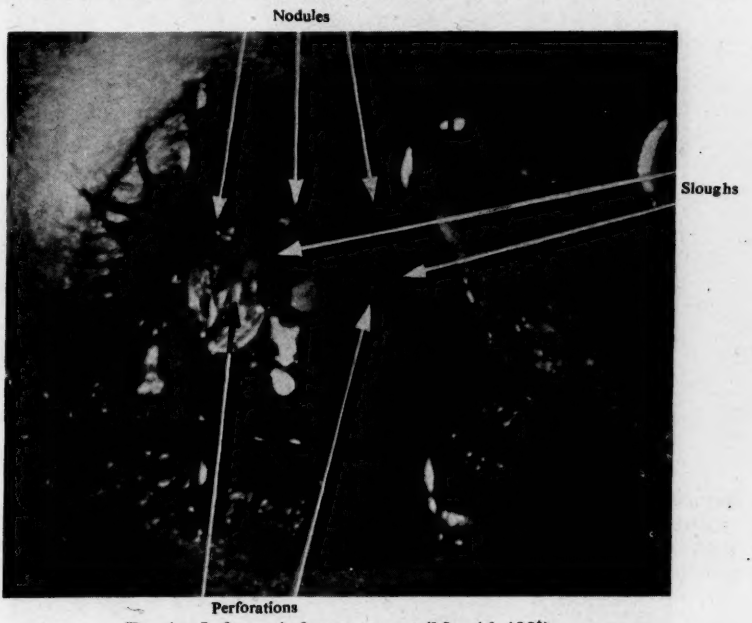


FIG. 1.—Left eye, before treatment (May 16, 1950).

There was no indication of active tuberculosis; uric acid/creatinine ratio varied from 1.5 to 0.712/1; no significant alteration of blood cholesterol levels.

Therapy.—Treatment at first was purely symptomatic with atropine and local irrigations, and in general the lesions were seen to progress; further episcleral nodules appeared, disintegrated, and were followed by new scleral perforations. More scleral sloughs formed and those already present increased in size. Later, however (May 30, 1950), there were signs of an attempt at scleral regeneration in the formation of a very thin film of whitish tissue beneath the conjunctiva in the perforated areas. Under a hand lens it showed a fine fibrillar structure, and was apparently composed of fibrous tissue.

Cortisone was first begun (June 23, 1950) as hourly eye drops, a 1: 5 dilution of cortisone acetate suspension in normal saline being employed. Some sympto-

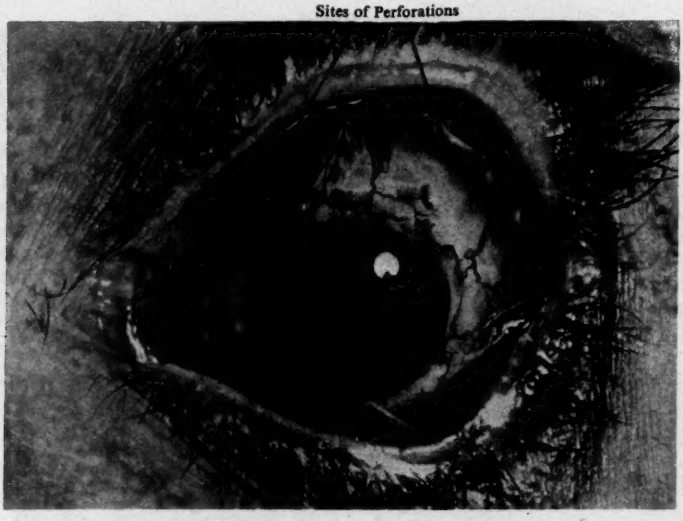


FIG. 2.—Left eye, one month after treatment (August 14, 1950).

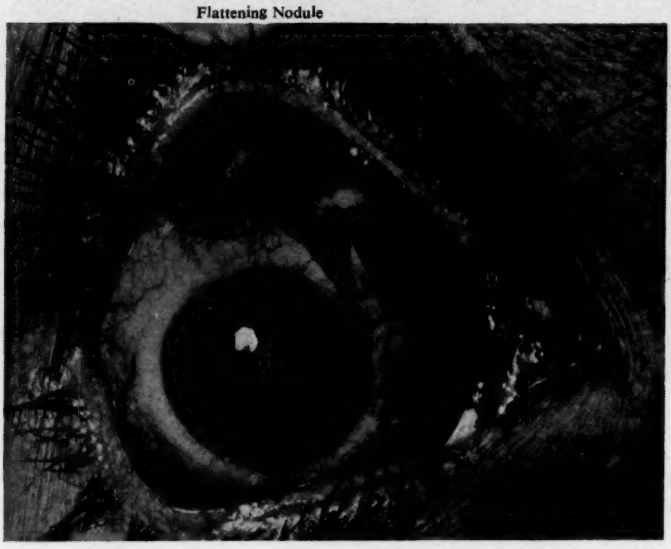


FIG. 3.—Right eye, one month after treatment (August 14, 1950).

matic improvement was experienced at once as a reduction of photophobia, and the conjunctival injection was reduced. During the 3 weeks of this administration there was a shrinking and flattening of the episcleral nodules with an increased formation of new fibrous tissue over several of the perforations, although a further new scleral

perforation appeared in one eye. Systemic treatment later became possible (July 14, 1950, to July 22, 1950) at a dosage of 100 mg. daily, and the healing process continued so that at the end of the week several of the perforations showed quite firm coverings of new scleral tissue. Figs 2 and 3 show the appearance of the eyes a month later, on August 14, 1950, and Fig. 4 shows a large temporal perforation of the left eye at the same time. Covering with new scleral tissue is almost complete, but the intermediate stage with a fine fibrillar appearance is still clearly seen in one area.

FIG. 4.—Left eye, one month after treatment (August 14, 1950).
Increased magnification shows early fibrillar appearance of new scleral tissue.

After the withdrawal of cortisone the conjunctival injection and photophobia returned within a day or so, but they were again abolished when administration was recommenced (September 15, 1950) with hourly cortisone drops and 100 mg. cortisone intramuscularly for 8 days. The essential ocular lesions showed a steady improvement with increasing scleral regeneration, but none of them completely healed and some showed little further change until the condition began to deteriorate in mid-December; fresh perforations and episcleral nodules appeared in both eyes (December 28, 1950), shortly before death occurred from septic pericarditis on January 12, 1951. Cortisone drops had been administered, 4-hourly from October 29, 1950 until one week before death. The right eye was obtained at *post mortem* for histological examination.

Histopathology of Right Eye.—Macroscopical examination showed a number of subconjunctival nodules in the upper temporal quadrant and irregular ulcerations in the anterior part of the sclera in the upper nasal quadrant of the eye. Scleral perforation had occurred at one point in an ulcerated area. Oblique sections were cut in order to demonstrate both types of lesion.

Sections.—An extensive ulceration of the nasal sclera is present immediately behind the region of the ora serrata. There is a deep necrosis of the scleral lamellae leaving only a thin irregular lamina of chronically infiltrated and partially necrotic sclerosed

FIG. 5.—Ulcerated area in scleromalacia perforans treated with cortisone. Although there is still considerable necrosis, fibroblasts are proliferating in the walls of the ulcer cavity, and the crater is covered by a thin membrane of newly-formed fibroblastic tissue. A few giant cells may be seen. Haematoxylin and eosin. × 50.

tissue overlying the choroid. The lips of the ulcer are infiltrated by chronic inflammatory cells among which a few giant cells are visible, and the crater is covered by a thin membrane of newly formed fibroblastic tissue (Fig. 5). The posterior walls of the ulcer cavity also show evidence of incipient fibroblastic proliferation. Areas of necrosis are present in the chronically infiltrated episclera behind the zone of ulceration, and the medial rectus muscle shows a marked infiltration by chronic inflammatory cells. Anterior to the ulcer, both the infiltrated sclera and the scarred peripheral cornea are markedly thinned. The anterior sclera on the temporal side of the globe is also chronically infiltrated and attenuated, and diffuse hyalinization of the stromal lamellae has occurred. Sections through the nodules in the upper temporal region show them to be situated in the outer layers of the sclera and in the tendinous expansion of the insertion of the external rectus muscle. They consist of masses of hyalinized and completely degenerate scleral and tendon fibres surrounded by a pale, clearly-defined zone of palisading fibroblasts which in turn is surrounded with a zone of chronic inflammatory cells, in which plasma cells and lymphocytes predominate while eosinophils and polymorphonuclears are notably few in number. A few nodules are present in the posterior half of the sclera on the nasal side (a most unusual feature in scleromalacia).

There is an early necrosis of the choroid underlying the ulcerated area where the differentiation between choroid and sclera has been almost completely obliterated but the retinal pigment layer is still intact. Scattered chronic inflammatory cells are present in the sclerosed iris and ciliary body, the pars plana of which shows marked atrophic changes. The lens is cataractous. The anterior choroid is atrophic, whilst posteriorly there is an advanced choroidal sclerosis associated with a chronic inflammatory infiltration in which one or two focal aggregations of pus cells are present. The retina shows some oedema in the nerve fibre layer, but the optic nerve shows no particular abnormality. The histological picture is that of *scleromalacia perforans*.

The sections described above were compared with histological preparations from six other cases of scleromalacia perforans not treated with cortisone, and areas showing approximately the same stage of the disease were selected for comparison. The following points were noted:

(*a*) The inflammatory reaction in the untreated cases was considerably more

FIG. 6.—Nodular area in sclero-malacia perforans not treated with cortisone. The inflammatory reaction contains neutrophilic and eosinophilic polymorphonuclears. Around the area of fibrinoid necrosis there is but little attempt at palisade formation. Cf. Fig. 7. Haematoxylin and eosin. × 90.

FIG. 7.—Nodular area in sclero-malacia perforans treated with cortisone. The inflammatory infiltration is mononuclear and there is a marked palisading of cells around the necrotic focus, in which some calcification has occurred. Cf. Fig. 6. Haematoxylin and eosin. × 70.

marked and contained large numbers of polymorphonuclears and eosinophils, whereas these cells were almost absent in the treated case.

(*b*) At the abrupt boundary between the fibrinoid material and the infiltrated sclera the untreated cases showed only moderate palisade formation and there was little fibroblastic proliferation (Fig. 6). In the treated case, however, there was a marked fibroblastic regeneration over the ulcerated areas (Fig. 5) and the palisade arrangement of the cells around the necrotic foci was more definite and more uniformly orientated. See Fig. 7 (above) and Fig. 8 (overleaf). Cortisone had not only inhibited the inflammatory reaction, but had also, to some extent, promoted repair processes.

(c) There was no evidence of cytoplasmic vacuolization or of cyst formation: the giant cells were somewhat more numerous in the treated case.

Discussion

In summary, our investigation shows that cortisone is able to exert a beneficial effect upon the lesions of scleromalacia perforans, as evidenced by a shrinking of the nodules and by scleral regeneration in the necrotic areas;

FIG. 8.—High-power view of Fig. 7, note marked palisading of cells and calcifying necrotic area. Such a high degree of palisading was not seen in six cases not treated with cortisone. Haematoxylin and eosin. × 120.

the histological examination indicates that these changes are due to an inhibition of the inflammatory reaction, particularly with regard to the neutrophilic and eosinophilic polymorphonuclear infiltration, and to a regeneration of fibroblasts.

It is interesting that Mundy and others (1951) came to almost identical conclusions from a similar study in a closely related condition. They performed three scleral biopsies on a case of rheumatoid arthritis with bilateral episcleral nodules, one being taken before and two during systemic treatment with cortisone. The histology was similar to that of scleromalacia. The nodules gradually decreased in size and by the fourteenth day of treatment were barely visible. Although these workers were unable to correlate this dramatic clinical improvement with a comparable degree of histological change, they noted that the cellular infiltration became predominantly mononuclear owing to a reduction in the numbers of neutrophilic and eosinophilic polymorphonuclears. The third biopsy showed proliferation of fibrocytes which, as in our case, tended to palisade around the fibrinoid necrosis.

A very complete study of the histological changes in rheumatoid nodules, both in the sclera and subcutaneously, has been carried out by Fienberg and Colpoys (1951). The occurrence of numerous rheumatoid nodules of the

sclera in a patient with advanced rheumatoid arthritis offered them the rare opportunity of removing such nodules at various intervals before and during the course of treatment with cortisone. It was also possible to study a scleral nodule, clinically 24 hours old, which appeared 32 days after treatment stopped. In addition, one half of a subcutaneous nodule of the elbow was removed from the same patient before treatment and the other half after cessation of treatment. The patient subsequently died and the recurrent scleral nodules and visceral rheumatoid nodules became available for study. Thus the investigation of Feinberg and Colpoys, as also that of Mundy and others, was superior to ours, in that they could compare the histological effects of cortisone upon the nodules with untreated lesions from the same patients.

To some extent the findings of Fienberg and Colpoys agree with ours and with those of Mundy and others, for they also observed an inhibition of the inflammatory reaction with diminished exudation and the development of a mononuclear reaction with a disappearance of eosinophils (which incidentally reappeared after cessation of treatment). During the course of treatment, they also noted the appearance of plump, elongated, rounded fibroblasts and an increase in the number of giant cells. Their report differs from ours in that they observed cytoplasmic vacuolization, and liquefaction in the foci of necrosis with central cyst formation, changes not seen in our sections.

More surprising was their finding that cortisone apparently produced a disorganization of the polarity of the palisaded cell layer, whereas our own evidence points in the opposite direction. In our preparations there was no question that the marked palisading and uniform orientation of the cells around the necrotic foci were considerably greater than in cases not treated with cortisone. No doubt further experience with cortisone in scleromalacia will elucidate this point; meanwhile such disparities in the histological findings may to some extent be explained by the fact that our own material is not strictly comparable with that of Feinberg and Colpoys. In their case, no perforations were present which had not advanced beyond the earlier nodular stage, and their dosage of cortisone was larger than ours. Furthermore, it is to be remembered that the details of disease reactions vary from case to case as do also individual responses to cortisone therapy. Indeed, several workers have found no histological alterations in rheumatoid nodules after ACTH or cortisone therapy (McEwen, 1950; Bauer, 1950; Ragan and others, 1949; Spain and Roth, 1951).

However, upon the three important features of the effect of cortisone in scleromalacia—namely, regression of nodules, inhibition of inflammatory reaction and fibroblastic regeneration—we all appear to be in agreement. That cortisone should inhibit the inflammatory reaction in these scleral lesions is exactly what one would expect for there is now considerable evidence to this effect in the literature (Duke-Elder and Ashton, 1951). It is thought that cortisone exerts this influence by preventing an increase in capillary permeability, which is an essential component of the vascular

phenomena in the inflammatory process. It is not, therefore, surprising to find a reduction in polymorphonuclear infiltration in the case treated with cortisone, for, to mention only one point, the diapedesis of these cells would obviously be obstructed; the fact that the mononuclear infiltration was but little affected suggests either that the cells appeared before treatment and had persisted in the tissues, or that they had migrated from adjacent lymphoid follicles. With regard to the marked reduction of eosinophils in the tissues, three possible explanations present themselves: cortisone eosinopenia; prevention of diapedesis; and modification of the hypersensitive state.

The fibroblastic regeneration in the case treated with cortisone is less easy to understand, for it is well known that cortisone depresses fibroblastic activity. However, this action is by no means absolute for it is related to the amount of cortisone given (Ashton and Cook, 1951); nor should it be forgotten that other factors tending to encourage fibroblastic regeneration are at work. Thus the ability of cortisone to damp down the reactivity of mesenchymal tissue is clearly of importance in controlling further fibrinoid changes in the connective tissue, thereby promoting conditions more favourable to repair processes. That ACTH and cortisone are able to inhibit fibroblastic repair in subcutaneous rheumatic nodules was shown by Hunt and Blanchard (1951); though these authors found an inhibition of fibrinoid alteration, there was a striking reduction in the proliferation of mesenchymal cells in the zone surrounding the central areas of necrosis. The fibrous regeneration was well marked in our case, despite the fact that complete healing was never obtained, but the dosage of cortisone administered was half that given by Hunt and Blanchard. It would appear, therefore, that cortisone, while suppressing the disease process, simultaneously inhibits repair, and the extent to which fibrosis eventually occurs depends upon the outcome of these opposing forces, which must obviously be related to the severity of the disease and to the dose of cortisone administered. These facts may explain the apparently contradictory evidence in the literature dealing with the effects of cortisone upon rheumatic lesions.

As is well known, spontaneous healing not infrequently occurs in rheumatoid nodules, and a case in which scleral nodules healed in such a way was described by Verhoeff and King (1938). A case reported by Friedenwald (1921) may have been of this nature. Feinberg and Colpoys (1951) compared the histological changes in their treated case with those found in eight rheumatoid nodules undergoing spontaneous involution, and concluded that cortisone induces an acceleration of involution and hastens regression by preventing the occurrence of further activity. While our findings lead us to similar conclusions, some modification of the statement of these last workers is required to explain the failure of cortisone to produce complete involution in all cases. It would probably be more accurate to say that, providing the disease process is not too severe or too advanced, cortisone may prevent further activity and so create suitable conditions for fibrous regeneration, a

process which, being inhibited in proportion to the concentration of cortisone present, will depend in extent upon the quantity of hormone administered. When sufficient cases of scleromalacia perforans have been treated with cortisone, it may become more apparent that this dual effect should be taken into account in deciding upon dosage.

Summary

(1) The literature dealing with scleromalacia perforans is briefly reviewed. It is believed that this condition should be regarded as belonging to the group of collagen diseases, and would be better named "rheumatoid nodules of the sclera".

(2) A case of scleromalacia perforans treated with cortisone is described, and the *post mortem* histological appearances of one eye are compared with eyes from six patients in whom such treatment had not been possible.

(3) Clinically, the administration of cortisone gave rise to a shrinking and flattening of the nodules with an acceleration of healing. There was considerable covering of the ulcerated areas with new fibrous tissue but none of the lesions healed completely.

(4) Histologically, the eye sections, when compared with those from the untreated cases, showed a marked inhibition of the inflammatory reaction, particularly with regard to neutrophilic and eosinophilic polymorphonuclear infiltration. The case treated with cortisone showed a much more marked fibroblastic regeneration, and the palisading arrangement around the areas of fibrinoid necrosis was more definite and more uniformly orientated.

(5) The findings are discussed in relation to other published reports, and it is concluded that in scleromalacia perforans cortisone prevents further activity and thus creates suitable conditions for fibrous regeneration, but that the regenerative process is inhibited in proportion to the concentration of cortisone present. With further experience it may become more apparent that this dual effect should be taken into account in deciding upon dosage.

Our thanks are due to Merck and Co., for a direct gift of cortisone. For the photographs we are indebted to the illustration departments of the Institute of Ophthalmology and the Royal Free Hospital, and we are grateful to Mr. V. Elwood for technical assistance, and to Miss E. Fitzgerald for secretarial help.

REFERENCES

ASHTON, N., and COOK, C. (1951). *British Journal of Ophthalmology*, **35**, 708.
BAUER, W. (1950). "Proc. First Clin. ACTH Conf., Chicago", ed. J. R. Mote, p. 355. Blakiston Co., Philadelphia.
CHRISTENSEN, L. (1951). *Trans. Amer. Acad. Ophthal. Otolaryng.*, **55**, 536.
DOUGHERTY, T. F. (1951). *Amer. J. Path.*, **27**, 714.
DUKE-ELDER, S., and ASHTON, N. (1951). *British Journal of Ophthalmology*, **35**, 695.
EBER, C. T. (1934). *Amer. J. Ophthal.*, **17**, 921.
FIENBERG, R., and COLPOYS, F. L. (1951). *Amer. J. Path.*, **27**, 925.
FRANCESCHETTI, A., and BISCHLER, V. (1950). *Ann. Oculist., Paris*, **183**, 737.
FRANÇOIS, J. (1951). *Ibid.*, **184**, 97.
FRIEDENWALD, H. (1921). *Amer. J. Ophthal.*, ser 3, **4**, 431.
VAN DER HOEVE, J. (1931). *Ned. T. Geneesk.*, **75**, 4733.
——— (1934). *Arch. Ophthal., Chicago*, **11**, 111.
——— (1948). "Lipoidoses and scleromalacia perforans". Noord-Holl U.M., Amsterdam.

HOLTHOUSE, E. H. (1893). *Roy. Lond. Ophthal. Hosp. Rep.*, **13**, 415.
HUNT, T. E., and BLANCHARD, A. J. (1951). *Ann. Rheum. Dis.*, **10**, 337.
KIEHLE, F. A. (1937). *Amer. J. Ophthal.*, **20**, 565.
KLEMPERER, P. (1950). *Amer. J. Path.*, **26**, 505.
——— POLLACK, A. D., and BAEHR, G. (1942). *J. Amer. med. Ass.*, **119**, 331.
KUHNT, H. (1912). *Z. Augenheilk.*, **27**, 146.
MALBRÁN, J. L., and MANZITTI, E. (1951). *Ann. Oculist., Paris*, **184**, 679.
MCEWEN, C. (1950). "Proc. First Clin. ACTH Conf., Chicago", p. 355. Blakiston Co., Philadelphia.
MUNDY, W. L., HOWARD, R. M., STILLMAN, P. H., and BEVANS, M. (1951). *Arch. Ophthal., Chicago*, **45**, 531.
OAST, S. P. (1937). *Ibid.*, **17**, 698.
RAGAN, C., GROKOEST, A. W., and BOOTS, R. H. (1949). *Amer. J. Med.*, **7**, 741.
ROCHAT, G. F. (1933). *Ned. T. Geneesk.*, **77**, 1935.
RUSSELL, J. A. (1950). *Bull. N.Y. Acad. Med.*, **26**, 240.
SORIANO, F. J., and RIVA, A. (1937). *Arch. oftal., B. Aires*, **12**, 139.
SPAIN, D. M., and ROTH, D. (1951). *Amer. J. Med.*, **11**, 128.
STILLERMAN, M. L. (1951). *Arch. Ophthal., Chicago*, **45**, 239.
SWAN, K. C. (1951). *Ibid.*, **45**, 630.
URRETS ZAVALIA, A , MALDONADO ALLENDE, I., and OBREGON OLIVA, R. (1937). *Arch. oftal., B. Aires*, **12**, 115.
VERHOEFF, F. H., and KING, M. J. (1938). *Arch. Ophthal., Chicago*, **20**, 1013.
WOJNO, Z. (1935). *Klin. Oczna*, **13**, 778.

Brit. J. Ophthal. (1952) 36, 385.

SUPRACHOROIDAL AIR INJECTION FOR DETACHED RETINA*

PRELIMINARY REPORT

BY

REDMOND SMITH

Moorfields, Westminster and Central Eye Hospital, London

INJECTION of air into the eye is considered by some authors to be useful in certain cases of detached retina (Spaeth, 1941). Where a considerable quantity of subretinal fluid has been evacuated, with consequent collapse of the globe, there are two ways in which the eye may regain its shape and tension. Either the subretinal fluid may re-form and reproduce the detachment, or aqueous may be formed quickly enough to restore the shape of the globe before subretinal fluid has collected in great quantity.

Presumably both processes tend to occur simultaneously. The crucial matter would seem to be the nearness of the retinal hole to the choroid at the stage when these structures have been rendered adhesive by diathermy. The union is tenuous in its early stages. The conception that the hole itself is " sealed " by diathermy seems difficult to accept, especially as in the case of a large hole it can still be clearly seen. The fact that the edges of the hole are adherent to the choroid may not be ophthalmoscopically obvious as the layer of " physiological glue " may be thick.

However, if the edges of the hole do become adherent to the choroid, the subretinal space becomes a closed pocket. It is no longer in direct contact with aqueous (*via* vitreous) and hence cannot be fed with high chloride osmotically active fluid. It may be that the boundary between the subretinal fluid and the chorio-capillaris is comparable with the blood-aqueous barrier. If this were the case, and the barrier was intact, the tendency might arise for fluid to be " secreted " into the space by the choroid by virtue of the fact that the subretinal fluid was osmotically active. This is purely speculative, but makes the basis for a rational concept of the peculiar phenomena associated with the formation and absorption of subretinal fluid and its variations.

The " blood-subretinal-fluid barrier " as a concept is useful in developing an argument to explain the behaviour of various types of detachment. In particular one wonders how it is that " spontaneous absorption " of fluid takes place after a retinal hole has been made adherent to the choroid. It would be of great interest to know whether the rate of absorption of such " residual detachments " is related to the degree of damage done at operation to the " blood-subretinal-fluid barrier ". Perhaps Bruch's membrane plus pigment epithelium, if left relatively intact over a wide area, retains chloride

* Received for publication February 25, 1952.

in the subretinal fluid. If this were so, the detachment would not settle, or would only settle slowly as osmotically active substances were lost from the small area of destroyed barrier membrane. Such would be the sequence of events in a detachment with, for example, much fluid below and a small hole above, which was coagulated with minimal diathermy reaction. Is it clinically a fact that a wider area of diathermy reaction (assuming the hole to be " sealed " incidentally) results in a quicker absorption of subretinal fluid? How is it that surface diathermy applied indiscriminately over a large retinal cyst (without puncture) can result in prompt absorption of the cyst. Does not the problem bear, in fact, a very close relationship to the problem of the action of cyclodiathermy in glaucoma? One might postulate in both that what was happening was the destruction of an area of highly selective barrier tissue between blood vessels and intra-ocular fluid.

This suggested mechanism for the absorption of subretinal fluid, *i.e.*, through a damaged barrier, might explain the well-known clinical phenomenon of delayed absorption after scleral resection. The edge of the resection being at the edge of the pocket of subretinal fluid a very large area of undamaged barrier is left.

It would seem that factors most favouring the reposition of a detachment would be the prompt adhesion of retina to choroid at the site of the hole and the evacuation of fluid. In a case in which a large quantity of fluid had to be removed, and in which there was a risk that its re-formation would remove the tear from proximity with the choroid, it would seem justified to take steps to attempt to reduce the re-formation of fluid if only for the first few hours after operation to give the hole time to become adherent.

The injection of air to fill up a collapsed globe would seem to be one logical method (Rosengren, 1938).

The injection of air into the vitreous body has two disadvantages: it may damage the vitreous and it obscures the fundus view (Hughes and Cole, 1946).

In five recent cases I have injected air into the suprachoroidal space at a site remote from the site of diathermy and puncture for detached retina.

Method

The normal procedure of surface diathermy and puncture was completed and as much subretinal fluid as possible removed by suction.

Air (1.5 ml.) was injected into the suprachoroidal space through an incision 5 mm. from the limbus at the side of the globe opposite to the diathermy operation. The site of injection had been prepared before the globe was punctured for removal of subretinal fluid. A small scratch incision was made almost through the thickness of the sclera and a direct suture inserted, the loop being drawn out a little, as in a direct pre-placed corneo-scleral suture. Subretinal fluid having been withdrawn from elsewhere, a fine hypodermic needle was cautiously introduced, its bevel facing the choroid, and air was injected as the last scleral fibres were pierced (Fig. 1). The immediate result in each case was the appearance of a dark choroidal detachment and the simultaneous escape of more subretinal fluid from the diathermy puncture (Fig. 2).

At this stage a quick inspection of the detached area was made and further diathermy applied if it appeared that the retinal tear was not surrounded. Reaction showed up well because in all cases the previously detached area was flat.

Within a few minutes the air was seen to be working its way all round the eye, until a ring choroidal detachment was

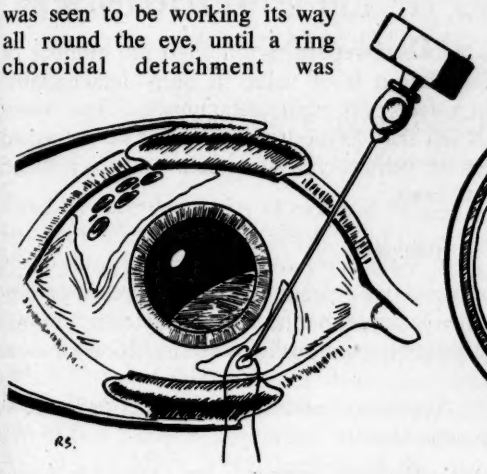


FIG. 1.—General view of air injection.

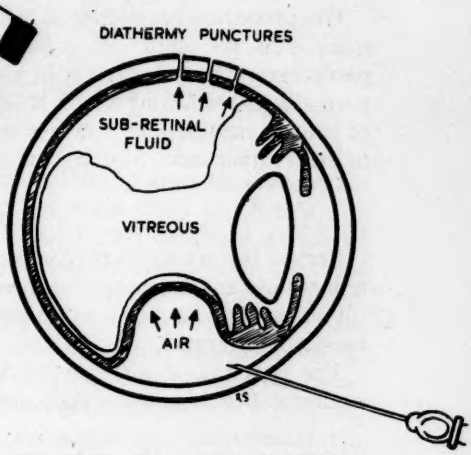


FIG. 2.—Expulsion of subretinal fluid by suprachoroidal air.

produced which precluded further view of the retinal tear if it was in a peripheral position. In some of the cases air escaped through the wound of entry. Secure suturing of this is advisable.

Results

The five cases operated on by this method were all of fairly poor prognosis and the results were encouraging.

(*a*) Four were cases of superior deep detachment in which the fluid did not absorb well on posture and in which the hole was not in close apposition to the choroid. Of these four patients, Cases 1 to 3 were over 60 years of age, and Case 4 was a high myope with chronic bronchitis. In Cases 1 and 2 the retina was reposed satisfactorily although one had a vitreous haemorrhage. At the present time (4 months after operation) this patient sees 6/36 and the retina can be seen to be flat. Cases 3 and 4 relapsed. This occurred in Case 3 after 3 months when she sneezed and the same hole and the same shaped detachment recurred within a few hours—a failure which might be attributed to inadequate diathermy adhesions. (This patient was later cured by a scleral resection by Mr. Frank Law.) Case 4 (the bronchitic) relapsed after 2 months with a new tear in a site remote from both the old tear and the air injection. This patient is at present awaiting re-operation.

(*b*) In Case 5 a residual detachment after one diathermy operation was found to have another retinal tear and could not be improved pre-operatively by posture. This retina was reposed satisfactorily with suprachoroidal air and further diathermy.

The procedure is thought to be worth reporting although the number of cases is as yet small. It is felt that it is of value in deep detachments, particularly where the tear is in a deep part of the detachment. Such cases normally give difficulty and it is felt that methods which might be suspected of being " meddlesome " in a more benign type of detachment are justified in these rather more troublesome cases.

Summary

Certain factors which may influence the formation and absorption of subretinal fluid are discussed. A plea is made for the recognition of a " blood-subretinal-fluid barrier " *and its possible relationship* with the blood-aqueous barrier is suggested.

The injection of air into the suprachoroidal *space is described and is* recommended in cases of deep detachments.

My thanks are due to the surgeons of the Moorfields, Westminster and Central Eye Hospital *for their kind permission to operate on* their cases and to use the facts in this paper.

REFERENCES

HUGHES, W. L., and COLE, J. G. (1946). *Arch. Ophthal. Chicago*, **35**, 525.

ROSENGREN, B. (1938). Acta ophthal. Kbh., **16**, 3.

SPAETH, E. B. (1941). " Principles and Practice of Ophthalmic Surgery ", *2nd ed., p. 822.* Lea and Febiger, Philadelphia.

Brit. J. Ophthal. (1952) 36, 389.

CASE NOTE

PANOPHTHALMITIS DUE TO AN ORGANISM OF THE BACILLUS SUBTILIS GROUP*

BY

ROBERT DAVENPORT AND CHARLES SMITH

Institute of Ophthalmology, London

THE first recorded series of cases of panophthalmitis due to *Bacillus subtilis* was that of Poplawska (1891), who described eight cases which followed perforating injuries, and 10 years later Römer (1901) described a case of post-operative infection. Reviewing the ocular infections due to these organisms, François (1934) collected forty cases from the literature; other cases have been reported by Greenspon (1918), Motolese (1936), and Reese and Khorazo (1943). In all these cases the organism was described as *Bacillus subtilis*, probably owing to the confusion that existed in the classification of this group of organisms, and no further identification was attempted. Wilson and Miles (1946) include all the pathogenic strains of this group, other than *Bacillus anthracis*, under the name of pseudo-anthrax bacilli or *Bacillus anthracoides*: the one exception to this classification is the *Bacillus subtilis* which according to them may be pathogenic in the eye but non-pathogenic in extra-ocular tissues and in laboratory animals. More recently Bergey (1948) has emphasized the confusion that exists in this group and has proposed a more rational basis for the identification of individual species. Chu (1949) suggested that many of the organisms which gave rise to infections were strains of *Bacillus cereus* and that the toxin which this organism produced might be responsible for their pathogenicity.

An outstanding feature of the ocular infections caused by these organisms is their fulminating character, the onset of symptoms occurring between 6 and 24 hrs of injury in most cases. The following case which was typical of those previously described provided the material for a more complete bacteriological identification of the organism isolated, and it has been possible to show that the organism is not a *B. subtilis*, but a closely allied organism, namely *B. cereus*.

Case Report

The patient, a Lebanese merchant, aged 29, living on the Gold Coast, was watching a repair to his motor car when he was struck in the right eye by a foreign body, while the mechanic was tapping the gear box with a hammer. The injury occurred at about 10.30 a.m. on January 19, 1952. A small haemorrhage was noticed on the outer part of the globe and although he felt no pain he went to the Government Hospital. He was seen at about 2 p.m. by the ophthalmic specialist and was given hourly drops (? sulphonamide), but the presence of a retained intra-ocular foreign body was suspected.

* Received for publication March 25, 1952.

By 7 p.m. that day he was in pain and vision had begun to fail. At 10 p.m. the eye was 'blind', and from this and the inflamed appearance of the eye he realized that it was irreparably damaged. He was advised to get an air passage to London, but owing to a plane cancellation could not leave until January 21, and did not arrive at Moorfields until January 22, 1952. During the delay in reaching London the inflammation became worse and the eye was "bleeding".

On admission to hospital he was febrile and somewhat exhausted but his general condition was good. There was gross chemosis and swelling around the right eye which was proptosed and obviously hopelessly infected. The centre of the opaque cornea had broken down and blood with a little thin pus was oozing from the necrotic opening.

X-ray examination showed the presence of an opaque intra-ocular foreign body; this was removed by a hand magnet and the eye eviscerated. The sclera was much thickened and the globe filled by an almost solid coagulum representing the intra-ocular contents. Cultures were taken from the discharge through the corneal perforation and from the posterior part of the intra-ocular contents.

Aureomycin treatment was started and the subsequent settling was rapid and complete.

Bacteriology

Cultures taken from the eye during evisceration gave a heavy growth of an aerobic spore-bearing organism, no other bacteria being present. The bacteria were Gram-positive, motile, and non-capsulate; they were about 1×3–5μ in size and frequently formed short chains. The colonies were of a buff colour, with a rough surface and an irregular border, but on well-dried medium were not rhizoid. On blood agar plates there was a wide zone of β-haemolysis around the colony.

The organism was resistant to penicillin and sulphonamides but sensitive to aureomycin and streptomycin.

A culture from the eye drops used before arriving in England gave a heavy growth of *B. coli*. No aerobic spore-bearing organisms were present.

Biochemical Reactions.—The organism grew readily on simple media, but only a slight growth was found when citrate was used as the only source of carbon. Glucose, maltose, saccharose, dextrin, and starch were fermented in 24 hrs; there was a later fermentation of salicin, but lactose, xylose, and arabinose were not fermented after 7 days' incubation. Litmus milk was peptonized and gelatin liquefied and Nagler's reaction was positive. There was no growth in MacConkey broth, and the Voges-Proskauer and methyl red reactions were negative.

Dr. H. P. Chu of the Institute of Animal Pathology, Cambridge, kindly performed tests for the production of lecithinase and these were positive.

Pathogenicity.—Suspensions of the organisms in nutrient broth containing between 10^7 and 10^8 organisms per ml. were injected into adult albino mice in doses of 0.5 ml. Seven of the inoculated mice died in 18 hrs and at *post mortem* there were haemorrhagic peritoneal and pleural exudates and gross dilatation of the small intestines which were distended by gas. Cultures from the blood, peritoneum, spleen, and kidneys all gave a pure growth of the bacterium.

The remaining mouse became moribund on the 4th day and *post-mortem* examination revealed an extensive pneumonic consolidation of the lung and dilatation of the small intestines. Cultures from the lung were sterile and no

bacteria could be found in sections, and it is possible that the consolidation may have been due to the activation of one of the endemic mouse pneumonia viruses.

An intraperitoneal injection into mice of 0.5 ml. of a suspension of 10^6–10^7 organisms per ml. caused one septicaemic death in 24 hrs and one death due to pneumonic consolidation of the lung after 5 days. The two survivors showed no signs of infection but cultures from the peritoneum and spleens at *post mortem*, 7 days after inoculation, grew a few colonies of *B. cereus*. A tenfold dilution of this suspension produced no lesions in a group of four mice when 0.5 ml. was injected intraperitoneally, and cultures at *post mortem* were sterile.

When 0.1 ml. of a suspension of the bacillus containing 10^7 organisms per ml. was injected into the anterior chamber of a rabbit's eye, an acute inflammatory reaction developed within 6 hrs, and there was severe chemosis and iritis in 24 hrs. The reaction settled down quickly and by the 4th or 5th day after injection the eye returned to normal. When the same quantity of bacteria was injected into the vitreous, a haemorrhagic panophthalmitis developed within 18 hrs; sections showed the vitreous to be filled with Gram-positive bacilli.

Identification of the Organism.—Since Chu (1949) suggested that the pathogenic airborne spore-bearing bacilli were probably members of the *B. cereus* species and not *B. subtilis*, it seemed important to make certain of the identity of the present strain. The classification used to identify the bacillus was that of Bergey (1948). The important points which separate this bacillus from *B. subtilis* are its size, colony form, and staining when grown in glucose medium. Thus it is larger than *B. subtilis*, which is normally 0.7 × 2–3μ, the colony is not rhizoid, and a Gram stain from glucose medium shows much vacuolation, which according to Bergey (1948) is not found with subtilis strains.

Some other features are unlike typical *Bacillus subtilis* strains: the motility is sluggish and gives an impression of deliberation very unlike the rapid movements seen with subtilis, and the digestion of gelatin is much more rapid with this organism than it is with *Bacillus subtilis*.

The species to which this bacillus is most closely allied is *Bacillus cereus*, the chief discrepancy between it and the description of Bergey (1948) being that it gives a negative Voges-Proskauer reaction, while classical strains give a positive reaction.

Discussion

Infections due to aerobic spore-bearing organisms are rare, but in man these organisms may produce a particularly fulminating type of panophthalmitis when entering the eye, usually as a sequel to penetrating injuries. Considering the great frequency of perforating injuries, many of which are likely to be contaminated with organisms of this group, the rarity of these infections is remarkable. Two hypotheses can be put forward to explain those cases which do occur:

(*i*) the infection is related to a dosage factor, panophthalmitis developing only when a massive inoculum enters the eye,

(*ii*) the power to produce such an infection is restricted to an uncommon member of this group of organisms.

The evidence in favour of the first hypothesis is that even with a toxin-producing organism, such as *Bacillus cereus*, a large inoculum is needed to set up an infection. The alternative theory that these infections are due to a single species of organism was put forward by Chu (1949), when he showed that strains of *B. cereus* produced a toxin, lecithinase, similar to the toxin of *Cl. Welchii*. This is the more attractive theory, but the evidence for it is not conclusive in cases of panophthalmitis, as *B. cereus* has never been identified in such infections before the present case and the strains previously isolated have not been tested for lecithinase production. There are, however, points which suggest that the theory may be correct:

(*i*) Greenspon (1918) isolated pathogenic bacilli from two cases of panophthalmitis and also from the operating theatre in which the infections occurred, but was unable to demonstrate pathogenicity in any *Bacillus subtilis* strain isolated from other sources, even when they were injected into the vitreous.

(*ii*) There is also a close similarity in morphology and pathogenicity between *Bacillus cereus* and the organisms in the cases reviewed by François (1934) which suggests that these bacteria are of the same species.

Against these observations must be set those of Kodama (1910), who isolated a bacterium from dust which could cause panophthalmitis in rabbits, but it should be noted that the organism he isolated came from a workshop in which a case of panophthalmitis had occurred following penetrating injury. Furthermore, the description of the organisms isolated in some cases differs widely from that of a classical *B. cereus;* thus Römer (1901) described a filamentous organism, difficult to culture, Reese and Khorazo (1943) say their bacillus was non-motile, Kodama (1910) described an organism which corresponds more closely to a classical *B. subtilis* than to a *B. cereus*.

Summary

A case of panophthalmitis due to *Bacillus cereus* is described. This organism has not been isolated previously in such a condition and it is suggested that many of the cases of panophthalmitis said to be due to *Bacillus subtilis* may in fact be caused by this organism.

Bacillus cereus is an organism which produces a toxin, lecithinase, which is probably the reason of the fulminating nature of these infections.

REFERENCES

BERGEY, D. H. (1948). "Bergey's Manual of Determinative Bacteriology", 6th ed. Ed. R. S. Breed, E. G. D. Murray, and A. P. Hitchens. Baillière, Tindall, and Cox, London.
CHU, H. P. (1949). *J. gen. Microbiol.*, **3**, 255.
FRANÇOIS, J. (1934). *Bull. Soc. franç. Ophtal.*, **47**, 423.
GREENSPON, E. A. (1918). *Amer. J. Ophthal.*, sec. 3, **1**, 316.
KODAMA (1910). *Klin. Mbl. Augenheilk.*, **48**, (*i*), 624.
MOTOLESE, F. (1936). *Boll. Oculist.*, **15**, 1023.
POPLAWSKA, S. (1891). *Arch. Augenheilk.*, **22**, 337.
REESE, A. B., and KHORAZO, D. (1943). *Amer. J. Ophthal.*, **26**, 1251.
RÖMER, P. (1901). *Ber. ophthal. Ges. Heidelberg*, **29**, 209.
WILSON, G. S., and MILES, A. A., eds. (1946). "Topley and Wilson's Principles of Bacteriology and Immunity", 3rd ed. Arnold, London.

CORRESPONDENCE

PTERYGIUM

To the Editors of the BRITISH JOURNAL OF OPHTHALMOLOGY

DEAR SIRS—Several books on ophthalmic surgery have appeared since Kamel described his method of dealing with pterygia (*British Journal of Ophthalmology*, 9, 549, 1946) but, as far as I am aware, in none is his procedure mentioned. In Cornwall, where pterygia are not uncommon, a number have been dealt with by the Kamel method with good result. As this procedure is simpler and apparently more effective than the transplanting methods still advocated, it would be interesting to know whether there is some objection to it, or otherwise why it has been ignored.

Yours faithfully,

WOODSIDE, WESTERN TERRACE, FALMOUTH. C. HEATH.

March 27, 1952.

ORBITAL IMPLANTS

To the Editors of the BRITISH JOURNAL OF OPHTHALMOLOGY

DEAR SIRS—D. P. Choyce in his article "Orbital Implants" (*British Journal of Ophthalmology*, **36**, 123, 1952) points to the advisability of using totally buried tantalum or acrylic implants, and concludes by saying that an effort should be made to develop an acrylic implant which would have the advantage of economy. His references to the literature do not include relevant articles by Ellis (1949), and Allen and Allen (1950), describing similar buried acrylic implants.

A few of these implants made by a dental mechanic to the specification of Allen and Allen have been used in the Birmingham and Midland Eye Hospital with satisfactory results. A case was shown at a meeting of the Midland Ophthalmological Society in December, 1951, in which movement of the prosthesis appeared to be full, although there was a 3° lag before the artificial eye began to move; this was followed by 15° comitant movement to right and left, after which more marked lagging occurred.

It would appear that implants of the type suggested by Allen and Allen would provide satisfactory movement for cosmetic purposes and could be used as a routine at excision. A small number for use in individual centres could quite easily be made by a dental mechanic, but an effort is being made here to have them manufactured cheaply on a larger scale.

Yours faithfully,

51, CALTHORPE ROAD, EDGBASTON, BIRMINGHAM, 15. M. J. ROPER-HALL.

March 21, 1952.

REFERENCES

ALLEN, J. H., and ALLEN, L. (1950). *Arch. Ophthal., Chicago*, **43**, 879.
ELLIS, O. H. (1949). *Amer. J. Ophthal.*, **32**, 990.

BOOK REVIEWS

Text-Book of Ophthalmology. Vol. V, The Ocular Adnexa. By SIR STEWART DUKE-ELDER. 1952. Kimpton, London. Pp. 1,082; 1,181 figs (32 col.). (90*s.*)

Sir Thomas Browne the beloved physician of Norwich would have studied this book with eager satisfaction. One can imagine him revelling in the descriptions of coko, morphoea, glomus, gangosa, milphosis, and mimical ectropion, because he was always agog to explore Nature's bypaths. Like Sir Stewart he was educated in three different universities, and he shared Sir Stewart's passion for assembling all the evidence about a subject, but here the analogy ends. To Sir Thomas the salamanders and basilisks of human legend were almost as real as Norfolk flocks, and if he had lived two centuries later he would have been at one with John Henry Newman who " used to wish the Arabian Tales were true ". Sir Stewart, on the other hand, never allows rarities and exceptions to entrap him into credulity or disproportion. His would-have-been red herrings never pass their minnowhood, and though he can exchange trifles with all Talleyrand's adroitness, he never loses the thread of his exposition. Therefore the fifth volume of this great text-book shows the same supremacy which was manifest in his previous writings.

Henry Kimpton is to be congratulated on having secured skilful printers, paper of high quality, and a binding worthy to enclose Sir Stewart's work. The tasks of arranging such a mass of material, and of planning the pages so as to show up the illustrations have been splendidly accomplished. There are many first-rate photographs from the Departments of Pathology and of Medical Illustration at the Institute of Ophthalmology in London, and some valuable pictures contributed by Rowland Wilson and Robert Wright, but the net has been widely cast, so that many fine illustrations have been lent by colleagues from other countries. Another commendable feature is the careful proof reading. Considering the size of the book, the number of misspelt words is negligible.

Volumes I to IV have been used as reference text-books by innumerable people, and this new volume will fulfil a similar purpose, because it contains all that the average ophthalmologist has ever seen or heard mentioned about the ocular adnexa, together with a multitude of hitherto unfamiliar things. No English-reading ophthalmologist, however, should be content to use the book merely for reference; and the reviewer, having read it from cover to cover, is left with a feeling of deep wonder that any man could accomplish so much. Sir Stewart begins with a masterly survey of developmental anomalies, and goes on to deal with diseases of the eyelids, lacrimal apparatus, and orbit. The final chapter discusses certain para-orbital structures, namely the nose, sinuses, nasopharynx, ear, and teeth, in relation to lesions of the eyes and their adnexa. If any one were to ask which parts are suitable for sampling it would be difficult to give him a satisfactory answer, because the level of Sir Stewart's performance is so consistently high. Therefore the proper way to treat this book is to read it from beginning to end, and then afterwards return to consult separate sections. Those who insist upon a preliminary taste might do well to read about the general aetiology and treatment of blepharitis (pp. 4952–4960) or cysts and tumours of the lacrimal gland (pp. 5247–5273), or let them take a substantial bite, and devour the magnificent description of orbital tumours (pp. 5526–5625) in which clinical and pathological facts are so lucidly conveyed. If our hypothetical sampler derives no thrill of satisfaction from any one of these sections then he must be empty of enthusiasm.

Those who begin to read Volume V with confidence in their own knowledge will suffer correction before turning many pages; and it would be amusing if we all had to endure a

viva voce on the contents. How many of us would have known anything about trichorrhexis nodosa, acanthosis nigricans, or bryocytosis ? Likewise, few among us were aware that *Wohlfahrtia magnifica* preys upon human eyelids, and that it is possible to catch tenonitis from a dog with distemper. We had all heard about ossification in the choroid, but now Sir Stewart reminds us that bone can also arise in the ruins of a chalazion. Yet his instruction is never portentous, and indeed the reader is from time to time lulled into the delusion that he knows much of it already. Plato would have approved that feeling, because he thought that knowledge is but remembrance, or, to cite Sir Thomas Browne's quaint Latinity, " reminiscential evocation, and new Impressions but the colouring of old stamps which stood pale in the soul before ".

Great Britain has reason to be proud of Sir Stewart as the author of what is probably the best text-book in any branch of medicine and surgery, but he himself would be the first to emphasize how much he owes to the ophthalmologists of other nations. Indeed his pages are adorned with many a tribute to colleagues all over the world, and he has already been made to feel at home in four continents. The fifth and most distant but by no means the least hospitable of the continents awaits the opportunity to welcome Sir Stewart, and Australasians will acclaim him all the more warmly because of Volume V. We are not likely to see a new book on ophthalmology worthy of comparison with it, until Henry Kimpton completes the distinguished sextet.

Significance of Heredity in Ophthalmology. By J. BRUCE HAMILTON. 1951. Pp. 135, 111 pedigrees, 20 tables, bibl. Massina, Melbourne. (50*s*.)

Tasmania has an area half that of England and Wales, and a population of less than a quarter of a million. This manageable population in a relatively unmanageable area is the subject of Dr. Bruce Hamilton's survey of the significance of heredity in ophthalmology. Among some 11,000 patients seen in his private practice in 17 years (1931–47), were 148 classified as blind. Of these, 81 were blind from congenital, hereditary, and developmental anomalies—amongst whom he includes fifteen cases of senile cataract. An introductory section on the types and modes of inheritance of genetic eye disease includes a discussion on education and welfare of the blind, and a plea for eugenic measures. The bulk of the monograph is given to detailed family histories; there are 111 pedigrees of eighteen genetic affections, amongst which squint and the refractive errors are included. There are useful pedigrees of the different varieties of cataract, glaucoma, nystagmus, Leber's disease, ptosis, and retinitis pigmentosa. Of special interest are those of a sibship with retinal detachment associated with cystic disease of the lung, of a woman and her niece with choroidal sarcoma, and of a family group with senile macular degeneration.

Dr. Hamilton has continued the work begun by Hogg in 1928, and his data form a useful beginning towards the full assessment of the frequency of genetic disease in a relatively closed community. That in this tedious work he should have found so much of considerable interest indicates not only the care with which the work was carried out, but also the significance of genetics in ophthalmology generally.

Genetics and Disease. By TAGE KEMP. 1951. Oliver and Boyd, Edinburgh. Pp. 316, 100 illus. (60*s*.)

Professor Tage Kemp's " Genetics and Disease " is the first comprehensive text-book on the subject in English. There are excellent treatises dealing with special aspects, but none which covers the whole field systematically. The readable " Introduction to Medical Genetics " by Fraser Roberts is devoted to general principles, whilst the two-volume treatise by Ruggles Gates deals largely with their application to the diseases of the different systems. Kemp's orderly treatise falls into five parts. The first hundred pages contain an excellent survey on fundamental principles; they comprise a mass of

information bearing on human inheritance that is fairly readily available elsewhere, but neither so systematized nor so concise. If there is any criticism, it is that conciseness in this section has been carried to an extreme, which may make these chapters rather difficult reading to the uninitiated. The methods and mathematics of medical genetics are discussed in the four chapters of the second part wherein essential information, available only in a scattered literature, is presented. The six chapters of the third part deal with the inheritance in man of normal traits, such as physiological features, blood grouping, and psychic qualities, a useful chapter being devoted to constitution and constitutional types. It is only in the last hundred pages that hereditary diseases are considered. The different systems are reviewed briefly and authoritatively. The three concluding chapters of the book, which constitute a fifth section, are devoted to genetic hygiene—a subject of immediate clinical importance, and one to which Professor Kemp has made outstanding contributions.

The book carries 100 illustrations, including both clinical photographs and pedigrees. This comprehensive and authoritative book should do much to stimulate clear thinking and productive work by clinicians. It is unfortunate that the translation from the original Danish is not quite adequate.

Manual of Orthoptics. By J. E. LANCASTER. 1952. Pp. 199. Thomas, Illinois. (40*s.*)

This volume provides an excellent groundwork for the orthoptic student. It deals chiefly with orthoptic diagnosis and treatment with an emphasis on the fact that the treatment is in itself a process of teaching and learning.

The manual is divided into two parts. The first part deals with orthoptic problems, including the selection of cases suitable for treatment. It is refreshing here to find a book of this kind severely critical; statements that no treatment is better than useless treatment, and that orthoptic training should not be used as routine treatment in unselected cases, are valuable. The second part deals with orthoptic techniques, which are explained in detail in a manner not covered by any other orthoptic text-book.

All would not agree perhaps with the suggestion that there is no hurry to give orthoptic treatment after operation; or with the idea of devoting six months' effort to correcting anomalous correspondence. The absence of explanatory diagrams is a drawback and definitions of the areas of Panum and of the Swan blind spot syndrome might well have been included. This book is, however, a very valuable and helpful contribution to the subject.

A Technique of Fitting Spectacle Frames. Published by the Association of Dispensing Opticians. 1952. Pp. 20, 2 appendices. A.D.O., London. (2*s.* 6*d.*)

This booklet is divided into four main parts:

(1) A statement of the basic measurements essential in fitting spectacles.
(2) A definition of the measurements.
(3) A way of obtaining the measurements.
(4) General notes of interest in relation to spectacle fitting.

The two appendices contain drawings of frames and lens shapes. The whole forms an excellent elementary guide to the fitting of spectacles.

NOTES

WORLD HEALTH ORGANIZATION

COMMITTEE ON TRACHOMA

The committee on trachoma appointed by the World Health Organization met at the Palace of the United Nations at Geneva from March 3 to March 8, 1952. The committee comprised G. B. Bietti (*Parma*), A. F. El Tobgy Bey (*Cairo*), F. Maxwell Lyons (*Gizeh*), Y. Mitsui (*Kumamoto*), H. Moutinho (*Lisbon*), Roger Nataf (*Tunis*), R. Pages (*Rabat*), P. Thygeson (*San Francisco*).

It was unanimously decided that Prof. Bietti should take the chair as President, and Prof. Thygeson and Prof. Mitsui were elected Vice-Presidents. The World Health Organization appointed Dr. J. M. Freyche as secretary to the committee.

The following items were on the Agenda:

(1) Chemotherapy and antibiotherapy of trachoma.
(2) Campaign against trachoma and associated infections.
(3) International trachoma prophylaxis.
(4) International co-ordination in scientific research.
(5) Miscellaneous items, the origin and classification of the diseases, keratoplasty, etc.

The report containing the various recommendations made by the committee will come before the executive council of the World Health Organization and will appear in the series of Technical Reports.

OPHTHALMOLOGICAL SOCIETY OF THE UNITED KINGDOM

ANNUAL CONGRESS, 1952

The 72nd Annual Congress of the Ophthalmological Society of the United Kingdom was held in Dublin, under the presidency of Mr. Maurice Whiting, on April 17, 18, and 19, 1952, at the Royal College of Surgeons in Ireland, as guests of the Irish Ophthalmological Society. The Society has made occasional extra-metropolitan excursions, the last having been to Glasgow in 1947, but only once before—in 1912—has it journeyed to Ireland. The success of this year's congress, at which over 125 members were present, makes it unlikely that so long an interval will be allowed to elapse again.

The meeting opened with a short speech by the President, in which he welcomed particularly Miss Euphan Maxwell, the only participant of the former congress in Dublin who was present; he thanked the President and Council of the Royal College of Surgeons in Ireland for the hospitality of their beautiful building.

The Montgomery Lecture, which is a regular feature of the Irish Ophthalmological Society meetings and therefore took the place of the Bowman Lecture on this occasion, was delivered by Professor Derrick Vail, an honoured guest from Chicago, who spoke on "Diffuse Collagenous Diseases with Ocular Complications". Professor Alan C. Woods of Baltimore, another distinguished guest, gave an address on "The Value of Cortisone and ACTH in Ocular Diseases", and Professor Henry Moore, Dr. F. S. Lavery, and Mr. E. G. Mackie followed with considerations of various aspects of that subject.

Among many interesting papers, particular mention may be made of Mr. T. F. Roche's striking observation that retrolental fibroplasia apparently does not exist in Dublin. A

demonstration on arteriography by Dr. Alan Mooney formed an apt background to his paper on "Perimetry and Angiography in the Diagnosis of Lesions in the Pituitary Region"; Dr. L. E. J. Werner discussed and demonstrated the problem of tonometric standardization; Professor Widdes and Mr. L. B. Somerville-Large arranged a beautiful Historical Exhibition of Irish Ophthalmology; and Dr. W. B. McCrea showed interesting pathological slides.

The kindness and hospitality of our Irish colleagues could not be surpassed. Our thanks are particularly due to Mr. L. B. Somerville-Large, who was mainly responsible for the great success of a happy and rewarding week.

TREACHER COLLINS PRIZE ESSAY, 1954

THE Council of the Ophthalmological Society of the United Kingdom has instituted a prize of £100, awarded triennially, for the best essay submitted upon a subject selected by the Council.

The prize shall be open to qualified medical practitioners of any nationality.
The essay shall be written in the English language.

The subject for the next award of the prize is "The Eye in General Vascular Disease". Dissertations concerned with a part of this subject will be received and considered on an equal footing with those concerned with the subject as a whole.

The closing date for entries for this award is December 31, 1953. Essays should be submitted to the Honorary Secretary, Ophthalmological Society of the United Kingdom, 45 Lincoln's Inn Fields, London, W.C.2, from whom further particulars may be obtained. No name should appear on the Essay, but it should be accompanied by a distinguishing pseudonym or quotation, written on the outside of a sealed envelope containing the candidate's name and address.

PRIZE COMPETITION

THE Ophthalmological Society of Egypt has decided to award a prize to the value of L.E. 20 for the most valuable contribution brought before the Annual Congress of the Society. Details may be had from the Hon. Sec., Dr. Mohammed Bey Khalil, Dar El Hekmah, 42 Kasr el Ainy St., Cairo, Egypt.

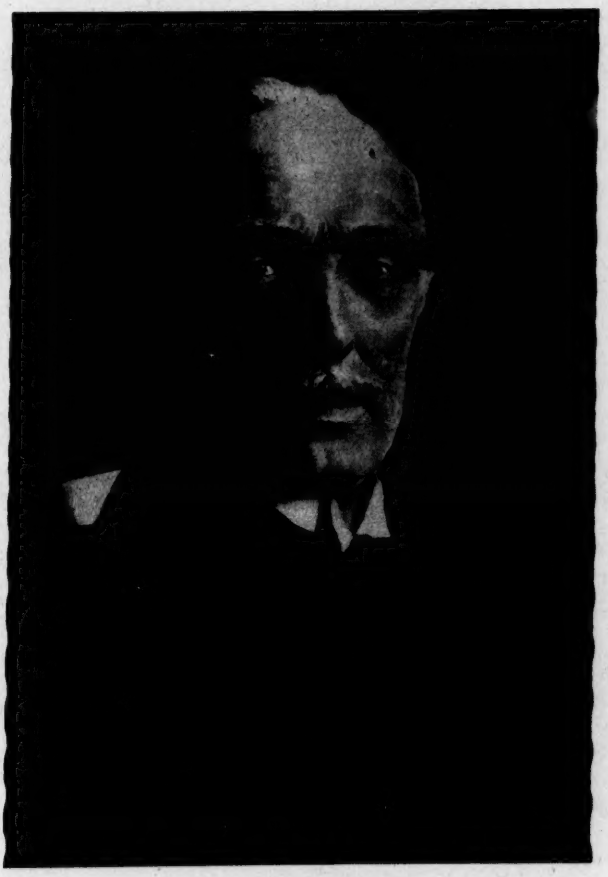
MR. J. W. TUDOR THOMAS, M.S., F.R.C.S., has been appointed President of the British Medical Association for 1953-54.

The Report of the Inter-Departmental Committee on the Statutory Registration of Opticians has now been published as a White Paper. H.M.S.O., London. (1s. 3d.)

OBITUARY

J. VAN DER HOEVE

THE whole world of ophthalmology has lost a great professional leader and a beloved friend by the death of Professor J. van der Hoeve. During the past few years his health was poor and he was becoming very frail, so that he fell victim to a road accident on April 26 last.



VAN DER HOEVE

Van der Hoeve was one of the leading figures in our specialty during the last half-century. Born in 1878, he graduated at Leyden University in 1900 when he became assistant to Professor Koster. In 1913 he was appointed Professor of

Ophthalmology at the University of Gröningen, and in 1918 he assumed the Chair of his old school in Leyden where the greater part of his life's work was done. His original contributions to ophthalmology during his long professional life were immense and continuous, and were recognized not only in his own country but throughout Europe. In Great Britain he held an honorary degree of the University of Edinburgh and was a recipient of the Sir William Mackenzie Medal for ophthalmic research. His Bowman Lecture in 1932 on Ocular Movements, a subject on which he wrote his doctorate thesis in 1902, will always remain classical. The breadth of his clinical interests and his unique ability to co-ordinate scattered observations were demonstrated by the fact that in the same year, in delivering the Doyne Memorial Lecture, he introduced the conception of " phakomatosis ", thereby integrating a number of syndromes characterized by their congenital origin, their hereditary incidence, and their widespread symptomatology in various parts of the body. His erudition outside the confines of his specialty was recognized by his being elected President of the Physical Section of the Royal Dutch Academy of Science in 1932.

To the present generation of ophthalmologists, however, van der Hoeve was probably known best for his influence in the international aspects of our specialty. A traveller to many lands and a welcome visitor in each, he was mainly responsible for the re-establishment of international relationships in ophthalmology after the disruption of the first World War, so that it was natural that in 1929 the first post-war International Congress should have been held in Holland under his chairmanship. At that time he was in the prime of his life and with his facility in languages, his genial courtesy, his unusual erudition, and his organizing ability, he stood out among his contemporaries as the universally acclaimed leader of his profession. Since that time his activity in international affairs and his immense capacity for making and maintaining friendships, as well as his professional excellence, progressively endeared him to a multitude of friends throughout the world, and these qualities were reflected in his being received into the honorary membership of some twenty national societies. In his later years, when physical frailties curbed his activities, he lost none of his endearing qualities, and now that he has gone he has left behind a universal memory unique in its intimacy and warmth.